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RENAL STONE DISEASE
Studies of epidemiology and calcium metabolism

by
SVERKER LJUNGHALL

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From the Department of Internal Medicine,
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To Kerstin , Per and Hannes

This summary is based on the following papers, which are referred to in the text by their Roman numerals.

- I Prevalence and incidence of renal stone disease in a health-screening programme
Sverker Ljunghall, Tony Christensson & Bo Wengle
Scand J Urol Nephrol, Suppl. 41, 39, 1977
- II Epidemiology of renal stones in a middle-aged male population
Sverker Ljunghall & Hans Hedstrand
Acta Med Scand 197, 439, 1975
- III Calcium, phosphate and albumin in serum. A population study with special reference to renal stone formers and the prevalence of hyperparathyroidism in middle-aged men
Sverker Ljunghall, Hans Hedstrand, Kristoffer Hellsing & Lars Wibell
Acta Med Scand 201, 23, 1977
- IV Urinary electrolytes in renal stone formers and healthy subjects. A population study of 60-year-old men
Sverker Ljunghall & A. Urban Waern
Scand J Urol Nephrol, Suppl. 41, 55, 1977
- V Mechanisms of hypercalciuria in recurrent renal stone formers.
Sverker Ljunghall, Ulla Backman, Bo G. Danielson, Gunnar Johansson, Bo Jung, Ragnar Källsen, Lars Wibell & Olov Wålinder
Scand J Urol Nephrol, Suppl. 41, 77, 1977

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Abbreviations

IHC	Idiopathic hypercalciuria
HPT	Hyperparathyroidism
PTH	Parathyroid hormone
cAMP	Cyclic AMP (adenosine 3',5'-monophosphate)
F_{Ca}	Fractional intestinal absorption of calcium
TRCa	Tubular reabsorption of calcium
TRP	Tubular reabsorption of phosphate

INTRODUCTION

Urinary-tract stone: a changing pattern

That stones may form in the urinary tract has been known for hundreds of years. It was so common among the ancient Greeks that a particular sentence was devoted to its treatment in the well-known rules of the medical profession, the Hippocratic Oath: "Neither will I cut them that have a stone but will leave this operation to those who are accustomed to perform it" (Hippocrates, 460-370 B.C.).

Even up to the last century, stone disease appears to have been almost exclusively due to bladder-stone formation. This sometimes occurred endemically, affecting large numbers of individuals. Stones in the lower urinary tract are nowadays also common in some under-developed parts of the world, e.g. Thailand and parts of India; in these countries, this is primarily a disease of children. In the industrialized part of the western world, the incidence of bladder stones has continually decreased during the 20th century and the disease is now rare, except for a few cases with outflow obstruction in the lower urinary tract. Parallel to this decrease, however, there is evidence of a marked increase in the formation of stones in the upper urinary tract. This change of pattern, which has been most extensively studied by Andersen (1969, 1973), has led to the suggestion that there is a causal relationship to equally significant and widespread changes in the external environment. As regards bladder stones, Andersen has advanced a working hypothesis that a major common factor may be a relative deficiency of animal proteins and/or fats, but there is at present no definite biochemical evidence for this hypothesis.

Thus, in the developed countries, stone disease is nowadays mainly the formation of stones in the upper urinary tract. In the following pages, therefore, there will be no discussion of the pathogenesis of bladder stones and these stones will no longer be included in the term "stone disease". No distinction will be made in this context between renal and ureteric stones; almost all of the latter apparently originate from the kidneys.

Our knowledge of renal stone epidemiology is far from complete. There is evidence of a continued rise in the incidence of stones but with considerable geographical variations (Andersen, 1969), indicating that, besides the post-

ulated effects of the raised standards of living, also local or regional factors may be involved. Confirmation of these hypotheses would be of importance in forming a basis for the further identification of possible pathogenetical factors at stone formation in the environment. However, so far, almost all the studies have been made on patients receiving hospital care. Several factors, besides the variations in the incidence of stone disease, may influence the hospital admission rates, and it may therefore be reasonably questioned whether hospital statistics accurately reflect the picture of renal stone disease in the population as a whole and whether such data are valid for the drawing of epidemiological conclusions. The general-health surveys, in which large numbers of individuals are examined, may provide an opportunity to study the epidemiology of selected disorders in a fairly unselected sample of the population.

Physico-chemical aspects of stone formation

Whatever the basic cause of stone disease - nutritional, environmental or genetic factors - the actual formation of a stone in the kidney may be looked upon as a strictly physico-chemical problem. Three major theories have so far been proposed to explain stone formation and growth.

The matrix-nucleation theory is based on the assumption that some matrix substance, e.g. a urinary mucoprotein (Boyce & Garvey, 1956), forms an initial nucleus for the subsequent growth of the stone by precipitation. However, although these supposed nuclei can be found in small amounts in all types of renal stones, their primary role in initiating the stone formation is not clearly established. Similar urinary microproteins will be found in the urine of non-stone-forming individuals and it appears that the protein matrix may just as well be a secondary inclusion adventitiously adsorbed on the faces of growing crystals (Vermeulen, Lyon & Fried, 1964). Also other substances have been proposed as nuclei for initiating calcium stone growth, such as brushite (Pak, Eanes & Ruskin, 1971) and uric acid (Lonsdale, 1968; Coe & Raisz, 1973).

The precipitation-crystallization theory implies that the supersaturation of urinary colloids eventually leads to their precipitation as a crystal, the critical particle which becomes trapped and subsequent crystal growth follows. This theory is virtually undisputed in the rare cases of urinary stones due to homozygous cystinuria, in xanthine stone formation and as regards uric acid

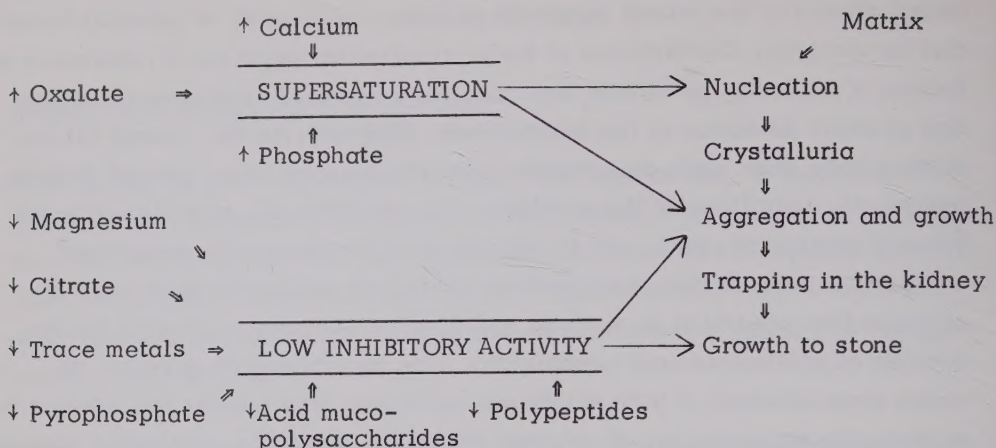


Figure 1. A model of calcium-stone formation, modified after Robertson (1976).

stones in hyperuricosuric subjects. All these are disorders in which the urine is clearly supersaturated with respect to the predominant constituent in the stone. It has been more difficult to apply the theory to the majority of stones composed of calcium and oxalate in individuals in whom the urinary excretions of these substances have been well within the normal range and in whom distinct supersaturation appears to be fairly rare.

The inhibitor-absence theory was suggested by the early findings that normal urine could hold larger amounts of crystalloids in solution than simple aqueous solutions. Several inhibitors of crystal formation *in vitro* can be identified in normal urine, such as small polypeptides (Howard, Thomas, Smith, Barker & Wadkins, 1966), pyrophosphate (Fleisch & Bisaz, 1964), magnesium (Hammarsten, 1929), citrate (Boothby & Adams, 1934), trace metals (Bird & Thomas, 1963) and acid mucopolysaccharides (Robertson, Knowles & Peacock, 1976). However, only sporadic cases have been shown to be due exclusively to the absence of inhibitor substance in the urine and its role alone as a major cause of common stone formations is not documented.

It is evident from broad, metabolic investigations of large materials of renal stone disease that there is no single factor, or perhaps even a single mechanism, that will by itself explain more than a limited number of all stone formations (Nordin, 1973). Modern thinking on the physico-chemical aspects of calcium stone formation therefore takes into consideration the relation between the super-saturation and the inhibitory activity. (Robertson, Peacock,

Marshall, Marshall & Nordin, 1976), both of which can be influenced by a large number of factors. A schematic model of this relation is shown in Figure 1. Supersaturation of the urine can be caused by an increased excretion of calcium, oxalate or phosphate, but, when the inhibitory activity is high enough, no crystallization will occur. However, if this activity is for some reason lowered, even a moderate supersaturation may be enough to initiate stone formation. The relative importances of the different factors in this relationship vary and the probability of crystallization at a given moment will therefore depend on the accumulation of unfavourable events. None of these, however, will per se necessarily be considered as clearly pathological, in the sense that they would not be found also in some non-stone-forming subjects.

A logical approach in the individual patient suffering from renal stone disease should therefore ideally include a detailed, clinical and metabolic investigation, in order to establish the dominating factor or factors in the pathogenesis of stone formation. In cases in which this is for some reason not possible or in which a fairly thorough study does not disclose any distinct abnormality, it follows from this concept of a balance between saturation and inhibition that either a reduction of one or more of the factors contributing to the supersaturation or an increase of the inhibitory activity will reduce the possibility of urine crystallization and subsequent stone growth.

Diagnostic classification of renal stone disease

Several disorders may be accompanied by the formation of stones in the upper urinary tracts. In Table I, some of the syndromes in which renal stones are not an unusual event are listed. The table also shows the estimated frequency of these disorders, based on a compilation of several stone materials (Lagergren, 1956; Herring, 1962; Prien, 1963; Lavan, Neale & Posen, 1971; Transbøl & Frydendal, 1973; Nordin, 1973; Coe & Kavalach, 1974; Danielson, Backman, Johansson, Källsen & Ljunghall, 1976).

As can be seen from Table I, most renal stones contain calcium as one major constituent. The following discussion of upper urinary tract stones is therefore primarily concerned with the calcium stone, mainly that composed of calcium and oxalate, as constituting the major problem in connection with idiopathic stones. The importance of the oxalate part will essentially be disregarded here and has also been less extensively evaluated in the literature,

Table I. Some disorders associated with the formation of renal stones

	Type of stone most commonly encountered	Mean frequency among recurrent stone formers, %
I Enzyme disorders		
Primary hyperoxaluria	Calcium oxalate	0.1
Xanthinuria	Xanthine	1/10,000
II Renal tubular syndromes		
Renal tubular acidosis	Calcium phosphate/oxalate	4 - 20
Distal type		
Proximal type	Cystine	1 - 3
Cystinuria		
III Uric acid stones	Uric acid	1 - 10
Gout		
Increased purine metabolism		
Hyperparathyroidism		
Idiopathic stones		
IV Stones associated with intestinal disease	Calcium oxalate	1
Jejuno-ileal bypass		
Inflammatory bowel disease		
V Infected renal stones	Magnesium ammonium phosphate	1 - 10
VI Hypercalcaemic disorders		
Hyperparathyroidism	Calcium phosphate/oxalate	3 - 10
Sarcoidosis		
Vitamin D overdosage		
VII Idiopathic hypercalciuria	Calcium oxalate/phosphate	40 - 50

partly because of the methodological difficulties of measuring oxalate. However, there are reports suggesting that variations of the urinary oxalate may often account for the transformation of the urine from a metastable, i.e. still not imperatively precipitating, to a supersaturated state (Robertson, Peacock & Nordin, 1971).

Calcium metabolism in renal-stone disease

Since the majority of the stones in the upper urinary tract contain calcium, attention has for many years been directed to the evaluation of calcium metabolism in nephrolithiasis. Flocks (1939) was the first to report that stone formers as a group, compared with controls, had a raised, urinary excretion of calcium. This is still the generally accepted opinion (Nordin, Peacock & Marshall, 1976), although it has not invariably been confirmed (Garrido, Jimenez, Damiano & Orozco, 1973; Welshman & McGeown, 1975; Jørgensen, 1975). One problem in the discussion has been to define the hypercalciuria. Since, in all studies, there is an overlap between stone formers and controls, it has never been possible to establish an upper limit of the normal range that will completely separate the two groups. The most widely used limit has been a daily excretion of 7.5 mmol in males and 6 mmol in females (Hodgkinson & Pyrah, 1958), but the mean + 2 SD value in the population is probably close to 10 mmol/24 hours (Morgan, Rivlin & Davis, 1970).

In some instances, a more or less well-defined cause of the hypercalciuria can be found, such as immobilisation, over-consumption of calcium or vitamin D or various states of hypercalcaemia. When the serum calcium concentration is elevated, this is generally due to primary hyperparathyroidism (HPT), which in most materials accounts for around 5-10% of all recurrent renal stone disease. When all the recognized etiologies of the raised urinary calcium have been excluded, the remaining part, which includes the majority of the cases, has been given the designation "idiopathic hypercalciuria" (IHC) (Albright, Henneman, Benedict & Forbes, 1953).

Idiopathic hypercalciuria (IHC)

The IHC syndrome covers normocalcaemia, hypercalciuria unexplained by an established cause and, at least in the original reports, a tendency to hypophosphataemia (Albright et al, 1953; Henneman, Benedict, Forbes & Dudley, 1958). Although this concept has been used for a considerable time, research

workers are far from unanimous as to the mechanisms that cause the raised urinary-calcium excretion.

Gastro-intestinal calcium absorption in IHC. Even in the first reports (Flocks, 1939; Albright et al, 1953; Henneman et al, 1958), it was noted that, in patients with IHC, the faecal calcium output was reduced. More recent studies, using isotope techniques, have further confirmed that most hypercalciuric individuals have a gastro-intestinal hyperabsorption of calcium (Pak, East, Sanzenbacher, Delea & Bartter, 1972; Nordin, Peacock & Wilkinson, 1972; Blacklock & Macleod, 1974). However, there are widely differing opinions as to whether this is a primary event or part of a generalized disturbance of the calcium metabolism.

Parathyroid activity in IHC. Tubular reabsorption of calcium. IHC resembles primary HPT, except that, by definition, hypercalcaemia is absent. Because of this resemblance and the known variability of serum calcium levels in cases of HPT, it has been suspected that many patients with IHC have instead a normocalcaemic variety of HPT (Wills, Pak, Hammond & Bartter, 1969). This theory has received further support from findings of a high proportion of abnormalities of parathyroid histology, adenomas or general hyperplasia, in series of recurrent-stone formers (Johansson, Thorén, Werner & Grimelius, 1975). The increased parathyroid activity suggested by these findings may theoretically be either primary, i.e. the basic cause is unknown, or secondary, compensating for increased calcium losses, in this context presumably of renal origin.

Some recent studies (Coe, Canterbury, Firpo & Reiss, 1973) maintain that faulty renal-calcium conservation accounts for a large part of IHC, thereby leading to a secondary HPT. In contrast with this view, it has been reported, from measurements made of the renal-tubular calcium reabsorption, that hypercalciuric stone formers in this respect do not differ from normocalciuric, stone-free controls (Peacock & Nordin, 1968).

A primary form of normocalcaemic HPT as a major cause of hypercalciuric stone disease has been proposed by Muldowney et al (1976). In their report, although the mean, total, serum calcium concentration was within the normal range, generally close to the upper limit, the ionized calcium was elevated concomitantly with raised concentrations of serum parathyroid hormone (PTH). It may, however, be questioned whether this syndrome is fundamentally

different from the hypercalcaemic form of HPT or the problem primarily one of defining the upper limit of the normal range.

Some of the discrepancies between the different reports are probably due to different selections of materials and also to the difficulties in the accurate evaluation of the parathyroid activity and determinations of ionized calcium. When measurements have been performed of the serum concentrations of PTH and the urinary excretion of cyclic AMP, the second messenger for the action of PTH (Chase & Aurbach, 1967), several studies indicate that most hypercalciuric individuals appear to have values well within the normal range (Smith, Thomas & Arnaud, 1973; Pak, Ohata, Lawrence & Snyder, 1974; Schwille, Schlenk, Samberger & Bornhof, 1976).

Bone resorption in IHC. Although most studies indicate that the increased amount of calcium appearing in the urine of stone-forming subjects originates from a hyperabsorption of the dietary calcium, an outflow from the body stores, primarily from bone, may theoretically also contribute. There have been reports of a reduced, bone-mineral content in hypercalciuric patients (Alhava, Juntti & Karjalainen, 1976) and calcium kinetic studies, indicating an increased bone resorption (Liberman, Sperling, Atsman, Frank, Modan & deVries, 1968). However, there is a general clinical impression that recurrent stone formers with long-standing hypercalciuria do not have a lasting, negative, calcium balance of clinical importance.

Vitamin-D metabolism in IHC. Our rapidly advancing knowledge of the importance of vitamin D in calcium homeostasis and the discovery that its most potent metabolite, $1,25(\text{OH})_2\text{-vit D}_3$, is the major regulator of intestinal calcium absorption (de Luca, 1974) raise questions concerning the role of vitamin-D metabolism in hypercalciuric, renal-stone disease. Only a few studies with a small number of patients have hitherto been reported (Shen, Baylink, Nielsen, Sherrard & Haussler, 1976; Gray, Caldas, Wilz & Lemann, 1976). In these, stone formers, compared with controls, had slightly, but significantly, elevated mean levels of metabolically active vitamin-D, although with a considerable overlap between the two groups.

Serum phosphate concentrations in IHC. In the IHC syndrome the tendency to hypophosphataemia has been a puzzling component. Although the first descriptions of the syndrome regarded the low serum phosphate concentration as a more or less obligatory feature, it has appeared from many subsequent

studies that the hypophosphataemia is an inconstant finding (Nordin et al, 1976). However, the presence of hypophosphataemia in IHC aroused further interest when it was reported that a low phosphate concentration in the renal-tubular cells was a stimulus to the conversion of vitamin-D into its metabolically active compound (Henry, Midgett & Norman, 1974). This may provide a reasonable explanation of the relationship between hypophosphataemia, calcium hyperabsorption and hypercalciuria but there does not appear to be a direct correlation between intestinal calcium absorption and the serum phosphate concentrations (Nordin et al, 1976). Thus, it is necessary to assume that further mechanisms act to reset the phosphate levels, e.g. there is a suppression of the secretion of PTH by the calcium hyperabsorption, if a low serum phosphate concentration is to be assigned pathogenetical importance in IHC.

Hypercalcaemia and hypercalciuria in stone disease: a summing-up

Hypercalcaemia, usually due to HPT, is found in 5-10% of all recurrent stone formers. Hypercalciuria is a common feature in normocalcaemic subjects, the prevalence being dependent on the choice of the upper limit of the normal calcium excretion. "Idiopathic" hypercalciuria may theoretically be due to an intestinal, hyperabsorption of calcium, a decreased, tubular reabsorption of calcium or an increased resorption of bone. Each of these mechanisms may occur alone or in combination with the others and either as a primary phenomenon or as part of a more fundamental disturbance of the calcium metabolism, mediated, for example, by the action of parathyroid hormone or by a disorder of vitamin-D metabolism.

At present, no single mechanism appears likely to account for all cases of IHC. As a reduction of the calcium output should be of benefit in the prophylaxis against stone recurrences, studies of the causes in the individual patients seem warranted, since the optimal treatment may prove to be different in the intestinal, renal and hyperparathyroid types of hypercalciuria.

AIMS OF THE PRESENT STUDIES

Attention has been focussed on some limited aspects of stone disease in an unselected population: (a) the incidence, prevalence and natural history of stones, (b) the prevalence of hypercalcaemia and hyperparathyroidism, and

Table II. Number of participants and participation rate in the three general-health surveys

Study no.	Sex	Age years	No. of participants	Participation rate (%)
I	Females	35-63	9,532	73.9
I	Males	35-63	4,960	74.9
II	Males	49-50	2,322	83.9
IV	Males	60	331	78.4

(c) the evaluation of hypercalciuria as a possible risk factor for stone formation. Furthermore, in a study of patients with recurrent calcium-stone disease, the relative importance of the different, theoretically possible mechanisms of hypercalciuria was investigated.

RESULTS AND DISCUSSION

Epidemiology of renal-stone disease (I, II, IV)

Subjects. Information on renal stone disease in the population was obtained in three different, general-health surveys performed in Stockholm (I) and Uppsala (II, IV), between 1970 and 1975. Table II shows the numbers of participants and the participation rate in each of the surveys.

Methods. All the participants in the surveys completed a standard questionnaire, in which one question was concerned with the previous experience of renal stones. This information was afterwards completed with personal interviews, postal questionnaires, scrutiny of hospital and out-patient records for the patients examined and an analysis of the hospital statistics for one year. Samples of non-participants in the surveys were also investigated in two of the studies (II, IV).

Criteria for stone diagnosis. In one study (I), the patient's own history of stone disease was accepted without further attempts at confirmation. More rigid criteria were applied in the two other investigations (II, IV). These included requirements that stones should have been visualized either (a) on X-ray or (b) at operation or (c) after spontaneous passage or alternatively (d)

that a tentative diagnosis of stones should have been made by a physician at the time of the characteristic clinical symptoms of renal colic.

Accuracy of stone diagnosis. It is apparent that, as far as accuracy in diagnosis is concerned, certain advantages are associated with the investigation only of patients admitted to hospital. However, less rigid criteria sometimes have to be applied in epidemiological surveys, particularly when it may be anticipated that the whole picture is not accurately reflected in hospital statistics. That the information collected by the present methods could be regarded as reliable was deduced from the following findings. In the two studies (II, IV) in which a critical evaluation of the patient's history was made, 75% of all cases of stone disease were verified according to criteria (a)-(c) above. Most of the remaining 25% of the subjects had experienced a single stone. The proportion of fully verified cases to those diagnosed on clinical grounds in these studies is in line with several reports from patients examined in hospital (Sandegård, 1956; Frank et al, 1959; Almby et al, 1976). Probably the lack of definite diagnosis in some cases is due to the fact that some stones are too small (crystal aggregates) to be visualized on X-ray pictures or at spontaneous passage.

Accuracy of screening methods. A few individuals in the health screenings who reported an initial history of stone disease did not acknowledge this at the follow-up. In all three studies, less than 0.2% of all participants thus had, by mistake, reported stones. Postal questionnaires sent to those in surveys II and IV who had not reported stones did not reveal any further cases. Analysis of hospital statistics and hospital in- and out-patient records did not disclose any stone former who had not been identified earlier through the screening questionnaires (II and IV).

When information was obtained from samples of the non-participants, it was found that the prevalence of stone disease, calculated from the replies to postal questionnaires or from hospital statistics, was not different from that among the participants.

Definitions. Prevalence of renal stone disease: The cumulative number of individuals who had ever experienced renal stones.

Incidence of renal stone disease: The number of individuals whose first experience of renal stones, had occurred during a given period.

Incidence of renal stones: The number of individuals with experience of renal

stones (first or recurrent stones) during a given period.

Recurrence of renal stones: If the latest stone had been experienced at least one year after the onset of stone disease, this was classified as a recurrence.

Stone incident: The clinical history was broken down into separate units (incidents), each representing one stone or a group of stones with continuous symptoms. If clinical symptoms were not terminated by the observed passage of a stone, all the symptoms during the following year were attributed to the same incident. Thus, only after a symptom-free period of one year were new symptoms considered to be due to the formation of a new stone. In the text, "stones" generally denotes "incident".

Prevalence and incidence of renal stone disease

The prevalences of stone disease in the male population in the three different studies were 8.9% (I), 13.7% (II) and 18.1% (IV), respectively. In females, the prevalence was significantly lower (3.2% (I)). When the different age-groups were compared, it was evident that the incidence of stone disease had increased considerably during the last 20 years, the average increase being at least two to three times. Thus, the prevalence of stone disease in the younger age-groups was two to three times greater than it had been in the older subjects at the corresponding age. This was true of both sexes. There were no differences in the incidence of stone disease between males and females up to the age of 30 but thereafter in females it remained fairly constant throughout, whereas in males it was more than twice as great. The average incidence of stone disease in males after the age of 30 was around 2% of the population during each five-year period (I).

When both first and recurrent stones were considered together, it was found that between 3% (I) and 8% (II, IV) of the male population had, during the last five-year period prior to the study, experienced a renal stone at least once. The corresponding figure for the females was around 1% (I).

The apparent differences in the prevalence and incidence figures between the studies were mainly due to the fact that the three surveys were not concerned with identically composed populations. When groups of the same age and sex were compared the differences were small, e.g. in 50-year-old men the prevalence of stone disease in the three studies was 10.1% (I), 13.7% (II) and 11.5% (IV) respectively.

These frequency figures for renal stone disease, are considerably higher than is generally appreciated. For example, in a large hospital survey (Boyce, Garvey & Strawcutter, 1956), about 0.1% of the entire population of the United States was annually admitted with renal stones. Similar frequencies have been reported from Great Britain (Anderson, 1964), Sweden (Almby et al, 1976) and other countries. The true prevalence of stone disease in the population has been estimated as about 1% (Ahlgren & Lörstad, 1965; Nordin et al, 1976). Our much higher figures, however, agree with the few available studies of selected population samples, giving approximate figures of prevalence of between 5 and 15% (Larsen & Philip, 1962; Scott, 1971; Westlund, 1973). Thus, the most reasonable explanation of the difference between hospital-admission rates and the figures derived from population studies is that all stone formers are not on every occasion admitted to hospital and therefore are not included in the hospital studies.

In one of the reports (I), this difference was estimated as about 50%, i.e. one-half of all stone formers were not registered at the hospital. It is likely that the proportion of non-admitted cases may vary considerably between different hospitals. Thus, possible geographical variations or variations with time should ideally only be analysed in well-defined samples of the population.

The continually rising incidence of stone disease in the population also causes an enlarged need for in-patient hospital care apparent from analysis of the hospital admission rates. Thus, the increasing incidence in the province of Uppsala reported by Hedenberg (1951) has continued. According to his large survey there was a ten-fold rise between 1911 and 1938 (the number of admitted cases this year 20/100,000 inhabitants). When the hospital statistics for 1969 were analysed (II) a further five-fold increase could be displayed. Thus, hospital admissions for renal stones nowadays are almost 50 times more common than in the beginning of this century.

Recurrences

Approximately 50% of all stone formers had experienced a recurrent renal stone at least once. The number of individuals with recurrences increased continually with the observation period, i.e. the time between the onset of stone disease and the study. In males, after a mean of 10 years, around 50% had at least one recurrent stone and after 25 years the frequency was close

to 75%. The recurrence rate in females was somewhat lower - 40% after 10 years and around 50% among those in whom the first stone had been experienced more than 25 years ago. Individuals with an early onset of stone disease and those with a family history of stone disease appeared particularly prone to develop recurrences. Whether the first stone had been passed spontaneously or had been operatively removed did not seem to influence the recurrence rate.

Stone formation is obviously not a singular event but a process in which the risk of recurrences remains for several years. Among unselected stone formers in these studies, the recurrence rate was of the same order as has been reported from patients initially admitted to hospital (Sutherland, 1954; Williams, 1963; Marshall et al, 1976; Williams & Chisholm, 1976).

Since several studies have reported considerable success in the prevention of stone formation by using different modes of therapy (Fleisch, Bisaz & Care, 1964; Prien & Gershoff, 1966; Coe & Raisen, 1973; Yendt & Cohanin, 1973; Smith, Thomas & Arnaud, 1973; Pak, Delea & Bartter, 1974), it appears desirable to distinguish the individuals who are at particular risk of early and repeated recurrences. From an epidemiological point of view, those with an early onset and those with a family history of stone disease constituted groups in which early clinical and metabolic investigations and attempts at the prophylactic prevention of recurrences may be indicated early in the course of the disease.

Natural history of the stone incident (II)

Up to the age of 50, 95% of all stone incidents in the males were terminated by spontaneous passage of the stone and altogether 12% of all stone formers had been operated upon for stone disease at least once. When surgical removal of the stone was necessary, ureteral surgery accounted for half of the cases, operations on the kidneys for 25% and endoscopic stone extractions for the remaining 25%. Only one individual had been subject to nephrectomy because of the complications of stone disease. There was a tendency for stones occurring after the age of 40 to require operation more often. Another finding was a smaller number of operations among those with frequent recurrences (4 stones or more). Among these individuals, 2.8% of all stones required operation, compared with 13.2% of the stones in subjects with few or no recurrences.

As expected, the frequency of operations was lower in the unselected stone formers of the present study than in materials obtained from surgical clinics. However, it appears also from studies of patients seeking hospital care that the majority of stones are passed spontaneously. Thus, a prospective study of patients with ureteral stones (Sandegård, 1956) disclosed that 82% of all stones were passed within 4 weeks, and in a recent Swedish study only 12.5% of all male stone formers from an emergency out-patient clinic were operated on (Almby et al, 1976).

Family history of renal stone disease (II)

A family history of renal stones, i.e. stone disease in at least one relative of the first degree, was twice as common in the stone formers (29%) than in stone-free, control subjects (15%). As a group, individuals with a family history of stones experienced earlier and more frequent recurrences. Among those in whom a possible cause of the stone formation was recognized, 23% had a family history of stones. In subjects with "idiopathic stone disease", 30% had cases of stone disease among their relatives, the frequency being highest in those with multiple recurrences (63%).

A higher-than-expected frequency of stone disease in relatives of stone formers has previously been suggested in some earlier reports dealing with the possible inheritance of renal stones (McGeown, 1960; Resnick, Pridgen & Goodman, 1968; Transbøl & Frydendal, 1973). Only a few causes of stone formation are definitely known to be genetically determined, e.g. cystinuria, and are too rare to disturb the overall picture in a population study. However, an increased prevalence of stone disease in relatives of stone formers does not necessarily imply a genetical basis, since first degree relatives also often share the external environment. The available information is not enough for a valid discussion of the relative importance of the genetical and the environmental factors.

One major difficulty in making an epidemiological approach to this problem is that many probands do not have precise information about stone disease in their relatives and it is not out of the question that a bias may arise from the fact that the stone formers have a heightened interest in stones amongst their relatives. Therefore, if an extended survey should be made to obtain first-hand information from all members of the families probably at least 1,000 individuals should be included.

Possible etiology of renal stones (II)

Most of the participants in the health surveys were free of symptoms at the time of the study and no systematic efforts were made to evaluate the etiology of stone formation retrospectively in the whole material. Determinations of serum calcium and uric-acid concentration were made in all subjects, as well as a qualitative test for cystinuria (Brand's test). Furthermore, all available information was collected from patients with hospital records, including stone analyses and pyelograms. Using these methods, a possible cause of the stone formations could be suggested in altogether 30 subjects, hyperparathyroidism being the most common (found in 7 individuals). Among the other diagnoses were three cases of medullary sponge kidney and three cases of cystinuria.

All three cases with a positive Brand's test had a quantitative cystine excretion of between 150 and 200 mg and all had passed calcium-containing stones at least once. These findings indicate that none of them had a homozygous trait for the disease (Knox, 1966). In this middle-aged, male population, the prevalence of cystinuria (positive Brand's test) was at least 0.1% ($3/2, 322$). Since the test was performed only on the stone formers, this is clearly a minimum figure, but it is in line with the data obtained by Lewis (1932), who found a positive Brand's test in $1/600$ out of ten thousand subjects.

Medical care for renal stone disease (II)

Altogether 23% of all the male stone formers up to the age of 50 had been admitted to hospital at least once. This corresponded to 3% of the entire male population. A further 7.5% of the population had visited an out-patient clinic at least once and 2.5% had called on other physicians because of renal stone disease. Analysis of hospital statistics for one year disclosed that around 175 per 100,000 males aged between 25 and 70 were this year admitted for in-patient treatment and 49% of them were operated on. The corresponding figures for the females were 75 admissions per 100,000, with an operation frequency of 39%. The mean duration of the hospital stay was 9 days.

Data on sick-listing were available as part of an epidemiological survey of 60-year-old men (Waern, 1977). In this population, in which the prevalence of stones was 18.1% (IV), during the last 10-year period 7% of all individuals had been sick-listed for an average of 17 days, including hospital admissions.

Renal stone disease ranked as no. 16 in the list of reasons for receiving sickness cash benefit.

The figures acquired in the present studies were obtained from a population with good facilities for medical care and obviously they do not necessarily reflect the picture of stone disease in general. The possible geographical differences in the incidence and prevalence of stone disease must also be kept in mind. However, a rough estimate could be made, using the information collected from all three studies (I, II, IV). This calculation suggests that, in Sweden, which has approximately eight million inhabitants, every year at least 25,000 males between 25 and 70 years of age experience renal stones. Half of them seek medical help, 5,000 are admitted to hospital for in-patient care and more than 2,000 operations are performed for renal stones. Altogether, approximately 10,000 of the males are sick-listed for a total of 100,000 days, including 50,000 days in hospital. Though less data are available for similar estimates relating to the female population, it seems reasonable to expect that the corresponding figures will be around one-third of those for the males. All these estimates are very approximate, but it is nevertheless apparent that renal stone disease has a considerable impact on the health services and that even a moderate reduction of the total incidence of stones would be of economic importance.

Calcium metabolism in renal stone disease (I, III, IV, V)

The serum concentrations of calcium were determined in all three health surveys (I, III, IV), thereby making it possible to estimate the prevalence of hypercalcaemia in unselected, renal stone formers. The urinary excretion of calcium, together with the output of other electrolytes, was measured in one of the studies (IV), primarily in order to investigate the importance of hypercalciuria as a risk factor in renal stone formation. Lastly, it appeared to be of interest to identify among recurrent calcium stone formers (V) which of the possible different mechanisms that may theoretically cause a raised, urinary calcium excretion was of the greatest practical importance.

Serum calcium concentrations: Prevalence of hyperparathyroidism (HPT)

When stone formers were compared with matched controls, no differences were revealed in the serum calcium concentrations between the two groups (III and IV) and the frequency-distribution curves were virtually identical.

Table III. Prevalence of hyperparathyroidism in three population studies

Study	Sex	Age	Prevalence of HPT (%) ^(a)		
			Entire population	Stone formers	Stone-free individuals
I	females	20-63	(0.6)	4.5	0.4
I	males	20-63	(0.3)	0.5	0.2
III	males	49-50	0.3	2.2	0
IV	males	60	0		

() data reported by Christensson, Hellström, Wengle et al (1976)

(a) HPT patients operated prior to the survey not included in study I

Thus, there was no tendency to any over-representation of high calcium concentrations within the normal range of the total serum calcium in the stone-forming group. In all three surveys, the frequency of HPT was higher among the stone formers (Table III). When the three studies were considered together, it was apparent that in males HPT rarely occurred before the age of 50 without concomitant stone disease. Among the altogether 3,798 males studied before this age, only three (0.1%) had HPT without stones.

It should be emphasized that all the neck explorations were performed on individuals with hypercalcaemia, although in several instances with only slightly elevated, serum calcium concentrations. It is not known to what extent some evidence of parathyroid disorder would be obtained if surgical exploration were more widely performed on subjects with normal serum calcium values.

In one of the studies (III), particular efforts were devoted to the adjustment of serum calcium concentrations for differences in the albumin content, using a factor derived from the population itself: $\text{Ca (adjusted value)} = \text{Ca (analysed value)} - 0.01 (\text{albumin} - 46.1)$. In this formula, 0.01 denoted the regression coefficient of the regression equation for the relationship between serum calcium and albumin. The mean albumin concentration in the healthy population was 46.1 g/l. This adjustment, however, had only minor effects on the distribution curves for serum calcium.

Serum and urinary phosphate (III, IV)

In both the population studies of middle-aged men, stone formers had a slightly lower, serum phosphate concentration than the matched controls. The difference, however, was not statistically significant. The frequency-distribution curves for stone formers were closely similar to those of the control subjects, i.e. there was no particular tendency to an accumulation of low values among the stone formers. Neither the urinary phosphate excretion nor the tubular reabsorption of phosphate, measured in a 24-hour collection, were different in stone formers and controls (IV). There was no correlation between the serum phosphate levels and the urinary excretion of calcium (IV).

These results thus support the view that hypophosphataemia, although a common feature in the first descriptions of IHC, is an inconstant finding in hypercalciuric stone disease (Nordin et al, 1976). Possibly a hypophosphataemic tendency, if present, is mainly apparent in subjects with more severe stone disease than is generally found in population surveys.

Urinary calcium (IV)

The 24-hour, urinary calcium was significantly raised in renal stone formers (mean $\pm$ S.D. 6.5 ± 3.5 mmol), compared with matched, healthy, control subjects from the same health survey (5.3 ± 2.8 mmol). The prevalence of stone disease was correlated to the urinary calcium, varying from 3.3% in the lowest to 26.7% in the highest percentile group of calcium excretion. Statistical analysis indicated that stone formers as a group were not accumulated in the upper part of the normal frequency distribution but rather constituted a population with an excess excretion of calcium of approximately 20% over the whole range of values.

The mean values for magnesium, sodium and potassium were not significantly different in stone formers and controls. There was a positive correlation between the urinary calcium and magnesium in both groups, but stone formers had a lower magnesium output for any given level of urinary calcium. A possible, protective role of urinary magnesium was suggested by the finding that individuals with the highest magnesium excretions had the lowest prevalences of renal stones. Furthermore, when subjects with similar urinary calcium outputs were compared, those with the lowest Ca/Mg ratios had the lowest pre-

valences of stone disease.

A raised, calcium output fulfilled all the criteria for a "risk factor", i.e. the mean value was raised in the affected group of individuals, the "risk" increased with increasing levels, and, a reduced output may reduce the recurrence rate (Pak, 1976).

This study refutes the recent suggestion that stone formers constitute the upper part of the normal distribution curve for urinary calcium (Nordin et al, 1976). The point of applying an arbitrary, upper limit of the "normal" calcium excretion is consequently questioned, at least in the sense of its constituting a watershed below which no attempts should be made to reduce the calcium output. Since the "risk" increased from the lowest values upwards, it rather appears as if any reduction of the urinary calcium will reduce the risk of stone formation. A rise in the urinary magnesium probably also acts in the same direction. The findings in this study are in good agreement with the previously described concept of the physico-chemical basis of stone formation (Robertson, 1976), in which an increased, urinary calcium increases the saturation and the urinary magnesium has an inhibitory effect on crystallization and subsequent stone growth.

Although it appears from the epidemiological studies that environmental factors associated with the generally raised standards of living probably are of importance for the increasing incidence of stones, there is at present no definite biochemical evidence for this hypothesis. A rise in the calcium output is one possible connection between the historical and physico-chemical views on stone formation, since an increasing calcium excretion has been noted in the population during the last few decades (Bulusu et al, 1970; Davis, Morgan & Rivlin, 1970), possibly as an effect of altered dietary habits, for example an increased consumption of carbohydrates (Lindeman et al, 1967) or protein (Morgen & Calloway, 1967).

Also for several other disorder environmental factors are believed to be of great importance for an apparent increase. One example of this is coronary heart disease (CHD), for which also a relationship to renal stone disease has been suggested (Westlund, 1973). However, in a separate study no such relationship could be displayed (Ljunghall & Hedstrand, 1976). In the same investigation also the dietary intake of vitamin D was analysed by means of a dietary questionnaire. This analysis did not disclose any differences be-

tween renal stone formers and controls from the same population, nor did recalculations of the data reveal any differences as regarded the intake of calcium, which for both groups was approximately 1 gram per day. Thus differences in the consumption of calcium or vitamin D are unlikely to be of major importance for the differences in calcium excretion between stone formers and non stone-forming subjects.

Mechanisms of hypercalciuria in recurrent renal stone formers (V)

As the previous population study (IV) indicated that all renal stone formers had, compared with matched controls, an excess excretion of calcium in the urine of approximately 20%, a study was performed to identify the mechanism responsible for this pattern. A series of 34 recurrent calcium stone formers consecutively referred to an out-patient, kidney-stone clinic was investigated. In all patients, the repeated determinations of the serum calcium concentration were within the normal range. A control group and a group of patients with operatively verified HPT were also studied.

The gastro-intestinal calcium absorption (F_{Ca}) was determined by an isotope technique based on the external measurements of ^{47}Ca in the forearm after intravenous and peroral administration of the radionuclide. The renal-tubular function was assessed by two different tests - the urinary excretion of beta-2-microglobulin for evaluating the ability of the proximal tubules to re-absorb low-molecular-weight proteins (Peterson, Evrin & Berggård, 1969) and the response to an ammonium-chloride loading (Backman, Danielson & Sohtell, 1976) for the detection of acidifying defects. The bone resorption was estimated by determinations of the urinary-calcium excretion after a 12-hour fast (fasting urinary calcium), according to Nordin, Peacock & Wilkinson (1972). Measurements were also made of the urinary excretion of hydroxyproline, a marker for the evaluation of metabolic bone disease (Laitinen, 1974). The parathyroid activity was determined by the measurement of the urinary excretion of cyclic AMP (cAMP). Particularly in the differential diagnosis of hypercalciuria, this cAMP assay seems to provide a better distinction between HPT patients and healthy subjects than the available methods of determining the serum concentrations of PTH (Wålinder, Ljunghall & Wibell, to be published).

The stone formers had a higher F_{Ca} (mean $\pm$ S.D. $72 \pm 15\%$), compared with healthy controls ($60 \pm 17\%$), and the intestinal calcium absorption was positively correlated to the 24-hour calcium. In both stone formers and controls,

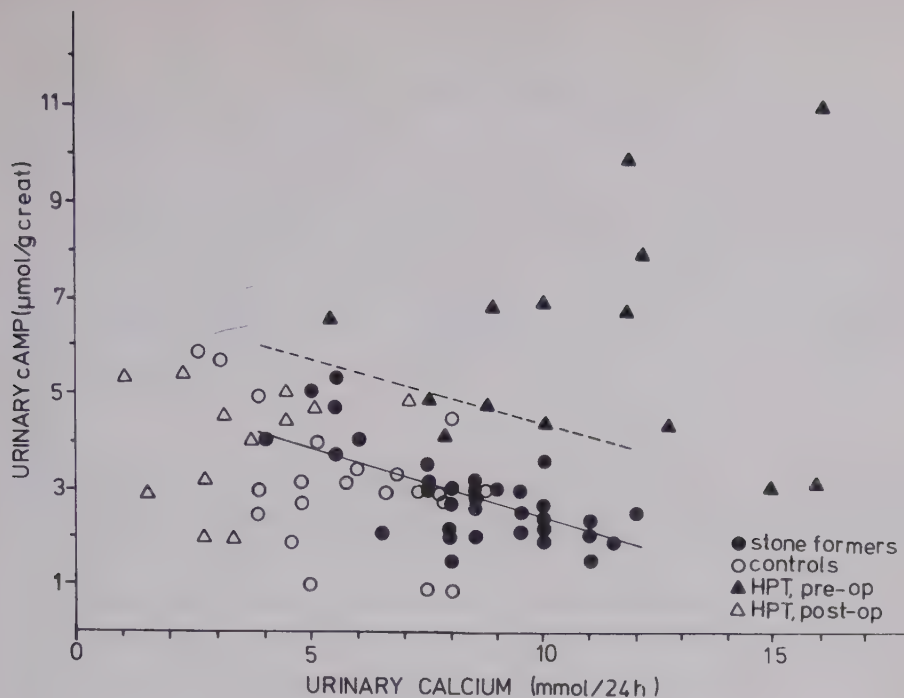


Figure 2. The relationship between the 24-hour urinary excretions of calcium and cyclic AMP (cAMP) in renal stone formers, healthy controls and patients with hyperparathyroidism (HPT), studied immediately prior to and three months after operation. The regression line for the stone formers is indicated (solid line) together with the mean + 2 S.D. limit (broken line) obtained from the controls.

the urinary excretions of calcium and cAMP were inversely correlated and the regression equations for this relationship in the two groups were closely similar. Patients with HPT had a higher mean cAMP excretion than both stone formers and controls, but post-operatively they appeared to fit into the same relationship (Figure 2). In the stone-forming group, the fasting urinary calcium was significantly elevated (0.34 ± 0.14 mmol calcium/mmol creatinine), compared with controls (0.25 ± 0.13). This suggested that an increased bone resorption could be an additional source of the raised urinary calcium. However, there were no differences in the urinary hydroxyproline excretions. In nine of the stone formers, there was some evidence of tubular dysfunction. This small group of patients did not differ significantly from the other stone formers, as regarded the urinary excretion of calcium and cyclic AMP.

This study gives further support for the idea that there is a substantial relationship between intestinal calcium hyperabsorption and hypercalciuria in recurrent renal stone formers. Together with the suggestions of an increased

bone resorption in some of the patients , the possibility of an underlying HPT must be considered.

When the diagnosis of HPT is established mainly by means of determinations of the total serum calcium concentrations , there are particular difficulties in evaluating patients with borderline values , because apparently a considerably proportion of them have HPT (Yendt & Gagne , 1968). It should therefore be emphasized that the present study only included individuals with serum calcium values clearly within the normal range.

In primary HPT , the tubular reabsorption of calcium (TRCa) is usually thought to be elevated and the hypercalciuria an effect of the increased filtered load. As a consequence of this , it has to be assumed that , in cases of normocalcaemic HPT , the ionized serum calcium is elevated , although the total serum calcium concentration is , by definition , below the upper limit of the normal. Since there is a significant positive relationship between the ionized and the total serum calcium (Lindgärde & Zettervall , 1971) , normocalcaemic stone formers with a primary HPT should be accumulated in the upper part of the normal frequency distribution of the total serum calcium. However , in the population study (III) , the values were almost identical in stone formers and matched controls. Furthermore , in the case of a primary HPT , the urinary calcium output would be expected to be higher for increasing levels of cAMP , instead of the inverse relationship obtained between the two parameters in the present study. Thus , stone disease appears not to be associated with a normocalcaemic HPT in this group of patients.

A primarily reduced TRCa is also unlikely to have caused the pattern observed in the present investigations. It was suggested that such a "renal leak" of calcium , postulated by Coe et al (1973) , was common in the development of hypercalciuria , with a secondary HPT following the urinary calcium losses. If one associates decreased serum calcium levels with states of secondary HPT , the hypothesis of renal hypercalciuria is opposed by the lack of difference in the serum calcium concentrations between the stone formers and their matched controls (III). Also , a positive correlation , instead of an inverse relationship , would have been expected between the urinary calcium and cAMP. From the present studies , it also appears as if other tubular defects , although commonly associated with recurrent stone disease (Backman , 1976) , are rarely of importance per se in the development of hypercalciuria or secondary HPT.

In conclusion, it is suggested that hypercalciuria in recurrent calcium-stone formers is usually caused by a mechanism independent of the action of PTH, through an increased intestinal absorption increasing the serum calcium levels postprandially (but not in the fasting state). This small rise will presumably be large enough to suppress the secretion of PTH and the excretion of cAMP. The increase in the filtered load, possibly together with a reduction of TRCa as an effect of the suppression of PTH, will cause an increased calcium excretion.

At present, the basic cause of this postulated sequence of events has not been identified. Among several lines for future research, the recent developments in our understanding of vitamin-D metabolism appear to be of particular interest in providing new and fruitful view-points on the problem of "idiopathic" hypercalciuria.

GENERAL SUMMARY

1. Information on the epidemiology of renal stone disease in the population was obtained from 17,145 individuals participating in three general-health surveys (I, II and IV).
2. Stone disease was more common in males than in females. Altogether 8.9% of the male and 3.2% of the female population had experienced at least one renal stone (I). The prevalence was greatest in middle-aged men, in 50-year-old males 10.1% (I), 13.7% (II) and 11.5% (IV) respectively. During the last five years prior to the study 3% of the entire male and 1% of the female population had passed at least one renal stone (I).
3. Close to half of all stone formers had experienced at least one recurrent stone after a mean observation period of ten years. The recurrence rate increased further when a longer time had elapsed after the first stone. Individuals with early onset of stone disease and those with a family history of stones were particularly prone to early and frequent recurrences (I, II).
4. Stone disease appears to be continually increasing in the population, the estimated increase during the last two decades being at least twofold (I).

5. The mean values and the frequency distributions of the serum calcium and phosphate concentrations were not different in renal stone formers and matched controls (III).

6. The prevalence of hyperparathyroidism (HPT) among unselected, male, stone formers was 2.2% and among those with recurrent stones 5.3% (III). HPT rarely occurred in males before the age of 50 without concomitant stone disease (I and III).

7. Renal stone formers had, compared with matched controls, a raised mean urinary calcium excretion. Analysis of the frequency distribution curves indicated that the two groups were shifted in relation to each other, stone formers having over the whole range of values an excess excretion of calcium of approximately 20%. Thus, the stone formers were not particularly accumulated in the upper part of the normal frequency distribution of urinary calcium (IV).

8. The prevalence of renal stone disease was correlated to the urinary calcium output, the difference being almost tenfold between the highest and the lowest calcium excretions (IV).

9. The mean values and the frequency distributions of the 24-hour urinary excretions of magnesium, sodium, potassium and phosphate were not different in renal stone formers and controls. However, individuals with a high magnesium output or with a low Ca/Mg ratio had a lower prevalence of stones, suggesting a protective effect of urinary magnesium against stone formation (IV).

10. Among patients with recurrent calcium stones hypercalciuria was mainly the effect of an increased, intestinal, calcium absorption. In this group of normocalcaemic subjects, there was no evidence of either a primary or a secondary HPT, the urinary excretion of cyclic AMP as a whole being inversely related to the calcium output (V).

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PREVALENCE AND INCIDENCE OF RENAL STONE DISEASE IN A HEALTH-SCREENING PROGRAMME

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ABSTRACT

Information on renal stone disease was collected from 14,492 individuals of both sexes, aged between 35 and 63 years, who participated in a general health-screening programme in Stockholm. Altogether 8.9% of all the males and 3.2% of all the females had experienced a renal stone at least once. The incidence of stone disease had increased considerably during the last 20 years, the figures for the youngest groups nowadays two to three times higher than in the oldest subjects at the corresponding age. Up to the age of 30 the incidence was similar in both sexes but thereafter significantly higher in the male population throughout. The overall recurrence rate was close to 50% after a mean observation period of 10 years and increased further in cases where longer time had elapsed after the first stone. During the last five years, 3% of the male and 1% of the female population had experienced renal stones. In the males this incidence was highest around the age of 50, whereas in the females it was reported by the youngest subjects. For both sexes it appeared that the incidence of stones was highest in individuals with an early onset of stone disease.

In altogether 2% of all the stone formers the serum calcium concentrations were elevated at the screening procedure and hyperparathyroidism diagnosed in a follow-up study.

INTRODUCTION

Most attention in renal stone research has been directed to the investigation of the metabolic factors that are responsible for recurrent stone formation. By far the majority of studies have been concerned with materials selected from patients receiving hospital care, and the picture of stone disease in the general population has been little explored.

From large hospital surveys, it has been calculated that the annual incidence of renal stones is about 0.1% (Boyce, Garvey & Strawcutter, 1956) and a common estimate of the total prevalence of stone disease in the population about 1% (Nordin, Peacock & Marshall, 1976). However, frequency figures more than ten times higher have been reported in the few epidemiological studies made of samples of the population (Larsen & Philip, 1962; Scott, 1971; Westlund, 1973; Ljunghall & Hedstrand, 1975).

The general health surveys, which include large numbers of individuals, offer opportunities to study the epidemiology of selected disorders in a fairly unselected population. In the present investigation, we have collected information on renal stone disease and calculated the prevalence and incidence figures in a screening programme comprising 14,643 individuals of both sexes, aged between 20 and 63, living in the City of Stockholm.

MATERIAL AND METHODS

Employees of the Stockholm City and County Council are offered free health screenings at regular intervals. This report presents data obtained from the 14,643 individuals, 5,020 males and 9,623 females, taking part in such an investigation during a two-year period, from July 1971 to July 1973 (participation rate 74%). The screening procedure has been explained in detail in a previously reported study mainly concerning the prevalence of hypercalcaemia (Christensson, Hellström, Wengle, Alveryd & Wikland, 1976). The examination comprised a physical and laboratory investigation including conventional chemical analyses of urine and blood samples. Subjects with a serum calcium concentration > 2.77 mmol/l (Auto-Chemist recorded) were selected for a follow-up study, when verified hypercalcaemia (VHC) was defined as a serum calcium concentration of > 2.70 mmol/l in two out of three analysed samples (Auto-Analyser). At the initial screening, 178 individuals had a

raised serum calcium according to these definitions; 172 of them were followed-up and in 95 cases the criteria for VHC were fulfilled. In 68 subjects this was diagnosed as being due to primary hyperparathyroidism (HPT), which was operatively verified in 45 of them. Altogether 16 HPT patients had a past or present history of renal stones (Christensson, Hellström & Wengle, 1976). In a further 14 hypercalcaemic patients, previously on thiazide treatment, did neck exploration reveal parathyroid adenomas. Four of them had a history of stone disease (Christensson, Hellström & Wengle, 1977).

The medical history at the screening was obtained by means of a standard questionnaire. One question dealt with renal stone disease and read: "Have you ever suffered from trouble with renal stones?". Altogether 771 individuals answered this question affirmatively. In the youngest age-group (20-31 years), which also had the lowest participation rate (50%), only four out of 151 subjects reported a history of renal stones. This small group was not further investigated. A postal questionnaire was sent to the remaining 767 individuals with questions about the age at the first and the latest experience of a renal stone. In 19 subjects, 1 man and 18 women, the history of renal stones given initially was not confirmed. A total of 578 individuals answered the questionnaire, giving a reply frequency of 77%. No further attempts were made to confirm the diagnosis.

DEFINITIONS

Prevalence of renal stone disease: The cumulative number of individuals who had ever experienced renal stones.

Incidence of renal stone disease: The number of individuals whose first experience of renal stones had occurred during a given period.

Incidence of renal stones: The number of individuals with experience of renal stones (first or recurrent stones) during a given period.

Recurrence of renal stones: If the latest stone had been experienced at least one year after the onset of the stone disease, this was classified as a recurrence.

Table I. Number of participants in a general health survey, prevalence of renal stone disease and reply frequency to a postal questionnaire according to age and sex

Age at survey (years)	Males			Females		
	Number of participants	Prevalence of stone disease n %	Reply frequency	Number of participants	Prevalence of stone disease n %	Reply frequency
58 - 63	1,584	146 9.2	81.4	2,895	67 2.3	82.1
54 - 57	1,163	105 9.0	78.3	1,820	64 3.5	75.0
50 - 53	1,098	111 10.1	82.0	2,228	87 3.9	70.1
45 - 46	378	34 9.0	67.7	875	25 2.9	68.0
35 - 41	737	46 6.2	71.7	1,714	64 3.7	76.6
All	4,960	442 8.9	78.7	9,532	307 3.2	74.9

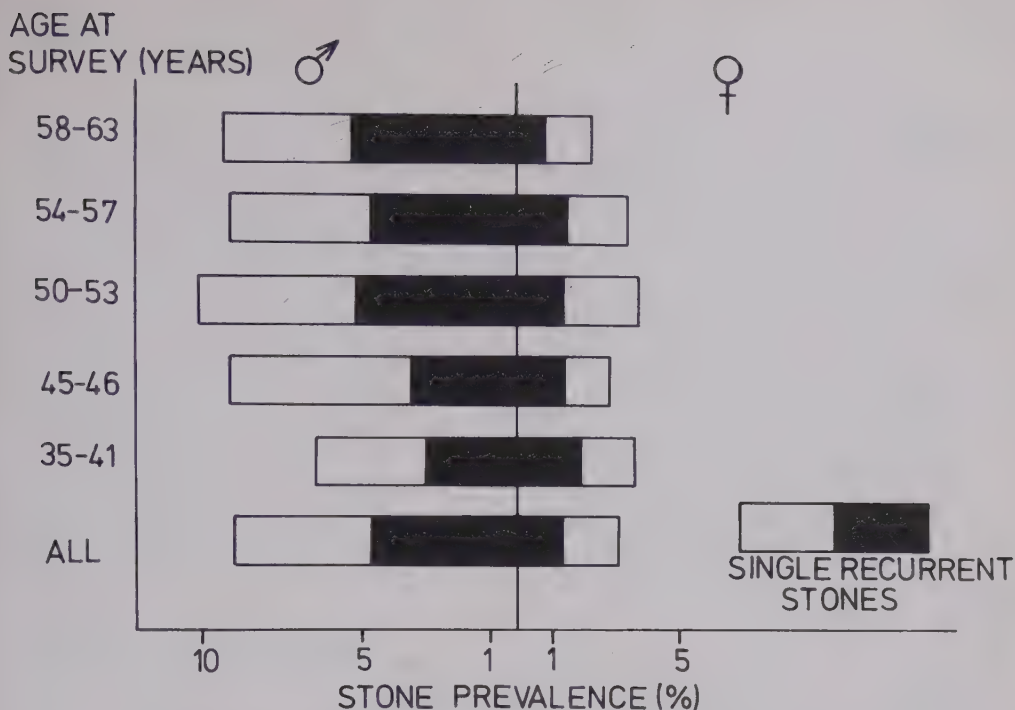


Figure 1. The prevalence of renal stone disease in a health screening of 14,492 individuals separated with regard to age and sex.

CALCULATIONS

It was assumed that those who answered the questionnaire were representative of all stone formers and frequency figures were calculated as percentage values of the entire screened population. The X^2 -test and the sign test were used for statistical analysis. The accepted level of significance was $p < 0.05$.

RESULTS

Prevalence of renal stone disease

Stone disease was almost three times more common in males (8.9%) than in females (3.2%) (Table I). In both sexes the greatest prevalence was found in the age group 50-53 years (10.1% and 3.9% respectively) but except for a less prevalence among the youngest males, there were no significant differences between the various age groups (Fig. 1).

Table II. Incidence of renal stone disease (% of the population) in relation to age

Age at onset (years)		-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59
<u>Age at survey (years)</u>										
Males	58 - 63	0.1	0.3	1.0	0.6	0.8	2.2	1.6	1.5	1.1
	54 - 57	0	0.3	0.6	1.5	1.6	1.0	2.1	1.8	-
	50 - 53	0	0.2	0.6	1.6	2.6	0.9	3.0	-	-
	45 - 46	0.3	0	1.6	2.4	1.6	3.2	-	-	-
	35 - 41	0	0.9	2.3	2.0	-	-	-	-	-
Females	58 - 63	0.1	0.1	0.2	0.3	0.2	0.4	0.2	0.2	0.2
	54 - 57	0.2	0.4	0.5	0.2	0.6	0.4	0.4	0.6	-
	50 - 53	0.1	0.5	0.9	0.5	0.5	0.9	0.8	-	-
	45 - 46	0	0.3	1.0	0.7	0.1	0.6	-	-	-
	35 - 41	0.3	1.3	1.1	0.4	-	-	-	-	-

Incidence of renal stone disease

The incidence of renal stone disease in the different age-groups during each five-year period is shown in table II and the prevalence curves, which demonstrate the sum of all the incidences, in Figures 2 and 3. The obtained data revealed that the incidence of stone disease had increased during the last 20 years, the figures for the youngest age-groups nowadays significantly higher than in the older subjects at the corresponding age. For example, 3.2% of the youngest male group had experienced onset of stone disease before the age of 30, compared with 1.4% of the oldest males. The corresponding figures for females were 2.7% and 0.4%, respectively. Up to the age of 30 the incidence of stone disease was not different in males and females. After that age the incidence was two to three times greater in the male groups, whereas it for the females remained fairly constant throughout.

Recurrence of renal stones

Among all the stone formers 49% had experienced at least one recurrence of stones after a mean observation time of approximately 10 years. The recurrence rate was higher in males (52%) than in females (44%) and corresponded to 4.6% of the entire male and 1.4% of the female population (Fig. 1). The number of individuals with at least one recurrence increased continually with the observation period, i.e. the time after the onset of stone disease (Table III) and the highest recurrence rate (77%) was thus obtained in males whose first stone incident was more than 25 years ago.

Incidence of renal stones

When first and recurrent stones were considered together it could be calculated that, during the last five years prior to the study, altogether 3.1% of the entire male and 1.0% of the female population had experienced at least one renal stone (Fig. 4). In males, there was a peak around the age of 50, the incidence in the group aged 50-53 years being 4.6%. The picture in the females was different, the incidence being highest in the youngest group and gradually declining with increasing age thereafter. Of all the stone formers, more than 25% of the males and 20% of the females had experienced one stone during the last five years (Table IV). For both sexes, this incidence was highest among individuals with an early onset of renal stone disease.

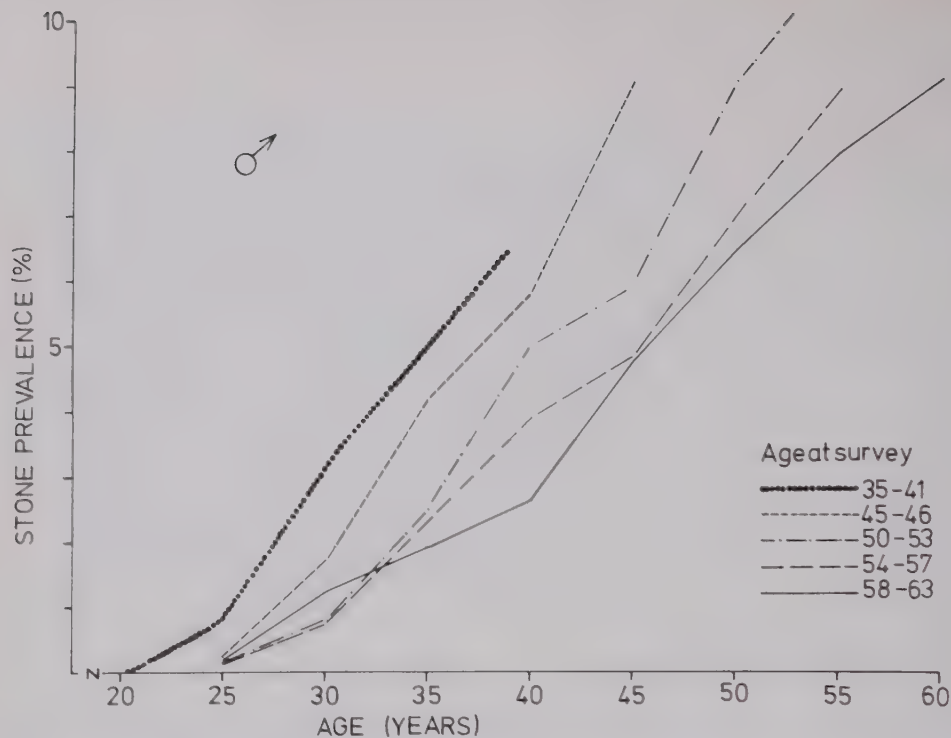


Figure 2. The prevalence of renal stone disease in relation to age in the male population.

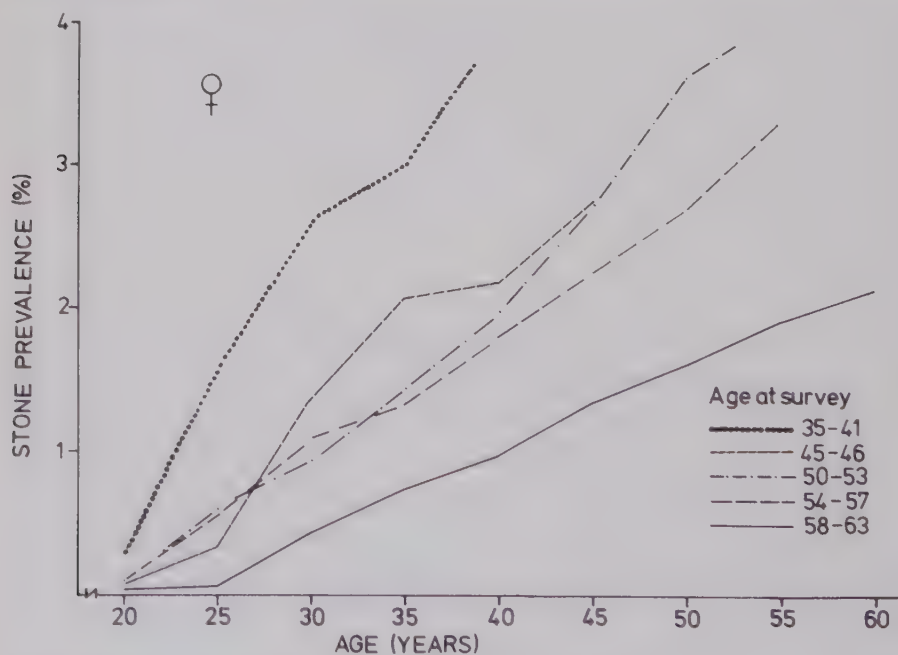


Figure 3. The prevalence of renal stone disease in relation to age in the female population. (Note that the scale of the vertical axis is different from that in fig. 2.)

Table III. Number of stone formers (%) with recurrence of renal stones in relation to age and observation time.
Each individual only included once in the table

Observation time (years)	5-9	10-14	15-19	20-24	25-	All
<u>Age at survey</u> <u>(years)</u>						
58 - 63	56	42	45	50	82	56
54 - 57	44	39	33	73	70	51
50 - 53	45	55	50	56	75	50
45 - 46	44	20	33	50	100	38
35 - 41	29	44	75	100	-	46
All	46	43	46	57	77	52

58 - 63	20	57	33	60	43	40
54 - 57	57	33	100	11	63	45
50 - 53	27	41	17	46	55	38
45 - 46	50	100	40	60	50	52
35 - 41	54	57	50	63	-	53
All	40	49	43	47	51	44

Females						

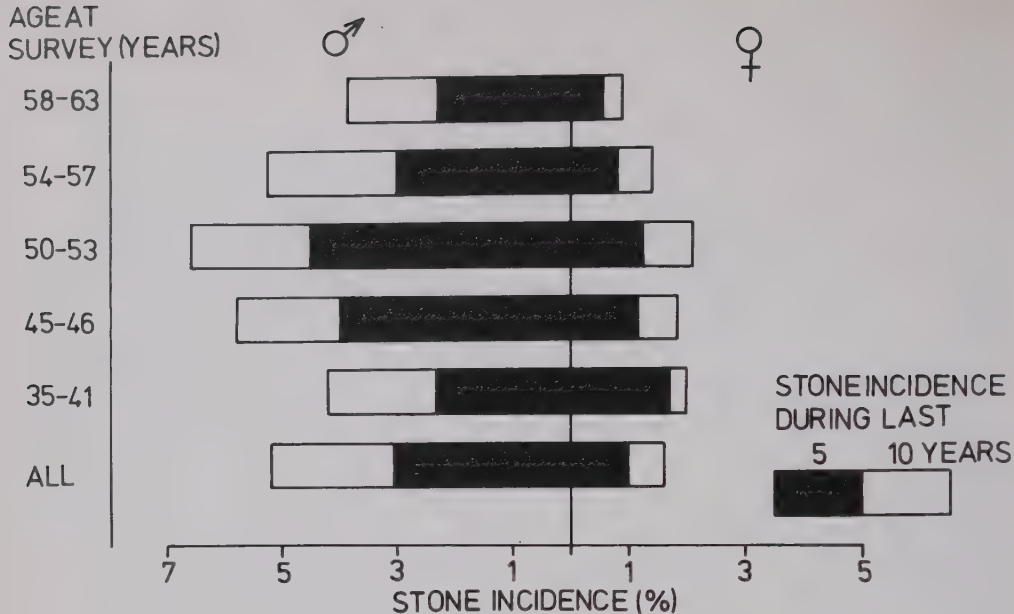


Figure 4. The incidence of renal stones (first and recurrent stones) in the population during the last five and ten years prior to the study.

Renal stone disease and hyperparathyroidism (HPT)

HPT was diagnosed in altogether 16 subjects (2 men and 14 women) with past or present evidence of renal stones, although not in all instances with a history of renal colic. If also these mainly asymptomatic cases are included this corresponds to a prevalence of HPT among all stone formers of 2% (0.5% of the males and 4.5% of the females). These figures only entail individuals in whom HPT was first diagnosed at the health screening and who did not belong to the group of HPT patients being treated with thiazides. Among the 77 subjects with raised serum calcium concentrations at the screening in whom verified hypercalcaemia (VHC) was not diagnosed at follow-up, significantly more than in the remaining population had experienced renal stones (19% of the males (5/26) and 10% of the females (5/51) respectively).

DISCUSSION

It is obvious that in a population study outside the hospital there is a risk of over- as well as under-estimating the occurrence of renal stones. Several investigations have shown that, in about 25% of all patients who present with a characteristic clinical picture, a definite diagnosis will not be established (Sandegård, 1956; Frank, deVries, Atsmon, Lazebnik & Kozwa, 1959; Almby,

Table IV. Incidence of renal stones (%) among the stone formers in relation to age at onset of stone disease

Age at onset (years)		20-29	30-39	40-49	50-59
Males	Stones during last				
	5 years	35	25	24	27
	10 years	45	36	38	40
	20 years	59	48	46	-
Females	-----				
	5 years	29	19	21	25
	10 years	36	26	32	25
	20 years	46	37	44	-

Meirik & Schöneberg, 1976). Since many of these cases later return with verified stones (Ljunghall & Hedstrand, 1975), they should probably be regarded as stone formers from the beginning. Asymptomatic carriers of stones, on the other hand, would not be detected in a survey of the present design. Probably such cases are rare and generally symptoms of a renal stone will appear within months of its formation (Powis, Black, Macdougall & Clews, 1974). Thus, it seems as if the symptoms of renal colic corresponds reasonably well to the occurrence of stones and on the basis of previous experiences of the acceptable reliability of the information about stone disease obtained through questionnaires (Ljunghall & Hedstrand, 1975; Ljunghall & Waern, 1977), no further attempts were made to confirm the diagnosis.

Hyperparathyroidism (HPT) is a well established cause for renal stone disease and among recurrent renal stone formers attending kidney stone clinics in most materials encountered in 5-10% of all cases (Lavan, Neale & Posen, 1971; Transböl & Frydendal, 1973; Coe & Kavalach, 1974). In the present study of an unselected stone-forming population, half of whom had only experienced a single stone, an overall prevalence of HPT of 2% was obtained. This is clearly a minimum figure since in this geographic area particular interest has been directed lately to the early diagnosis of HPT in renal stone disease, recently reported by Lennquist et al (1976), and it is probable that some earlier operated cases of HPT were not included in the present survey. It should also be underlined that in the present study only a single determination of the serum calcium concentration formed the basis for the follow-up

study and that besides this no attempts were made to disclose further subjects with possible HPT among the stone formers. The finding that individuals with elevated serum calcium levels at the screening, not sustained at follow-up, had a higher prevalence of stones suggests, however, that in this border-line group further cases of HPT may be concealed.

The prevalence of stone disease in this population was close to 9% of the males and 3% of the females and the incidence of stones during the last five-year period was around 3% and 1% respectively. These figures compare fairly well with the available data from selected population samples (Larsen & Philip, 1962; Scott, 1971; Westlund, 1973; Ljunghall & Hedstrand, 1975) but are considerably higher than is generally recognized on the basis of the evaluation of different hospital materials. Thus, in a recent study partly covering the same population as the present one, the annual incidence of stones in middle-aged males was around 0.2% and in females less than 0.1% (Norlin, Lindell, Granberg & Lindvall, 1976), the criterion for stone disease in their study being stones visualized on X-ray. Also when the difference for establishing the diagnosis was considered there remained an approximately twofold difference between their report and the present one, indicating that about half of all the stone formers were not included in the hospital study. This discrepancy seems to be of a reasonable proportion and agrees with the observation (Ljunghall & Hedstrand, 1975) that many stone formers, particularly those with frequent, recurrent stones, do not seek hospital treatment for each stone incident. Also, some individuals visit physicians outside the hospital. It is likely that this proportion of non-hospitalized stone patients varies between different hospitals and therefore comparisons between geographic areas or analyses of temporal variations will be hazardous, unless based on well-defined samples of the population.

In this population study it was found that stone disease affects a large number of individuals, the incidence appears to be increasing and the risk of recurrences high, remaining for several years after the first stone. Such a pattern could be expected if environmental factors were of increasing importance in the development of renal stone disease. This idea is also compatible with the historical view that stones in the upper urinary tract occurred only rarely before the beginning of this century but now appear to be gradually increasing throughout the industrialized world (Andersen, 1969; 1973). No single factor is likely to be solely responsible for this development, but several different consequences of the generally raised standards of living may be of

importance, such as alterations in dietary habits, working conditions or stress experience. For instance, a high urinary calcium, a probable risk factor in renal stone disease (Nordin, Peacock & Marshall, 1976) may partly be the result of dietary factors, among them, an increased consumption of carbohydrates and protein (Lindeman, Adler, Yiengst & Beard, 1967; Margen & Calloway, 1967). Also a raised urinary excretion of uric acid, a possible effect of a high intake of purine-rich foods (Hodgkinson, 1976), is associated with an enhanced tendency to calcium stone formation (Coe & Kavalach, 1974; Robertson, Peacock & Knowles, 1976). The urinary outputs of both these constituents is reported to have increased in the population during the last few decades (Bulusu, Hodgkinson, Nordin & Peacock, 1970; Hodgkinson, 1976).

If the association between the dietary habits and renal stone disease is so far only circumstantial, the importance of such factors as a sedentary life style and psychological and physiological stress is even more difficult to evaluate. However, there have been reports of an increased frequency of renal stones among individuals with no regular physical activity at work (Milbert & Gersh, 1943; Blacklock, 1969; Ljunghall & Hedstrand, 1976) and a relationship between stress and urolithiasis has also been suggested (Selye, 1946; Lennquist, Granberg, Nordström & Norlén, 1976).

Although there was evidence of a definite increase in the incidence of renal stone disease for both sexes during the last decades the pattern was different for males and females. In the female population the incidence was similar to that of the male before the age of 30 and fairly constant throughout the years, whereas in the males after this age the incidence rose significantly. Possibly both genetical and environmental factors are of importance for the development of this picture. If it is assumed that the major part of idiopathic stone disease is associated with environmental factors in the broadest sense, apparently these are of greatest importance in the males after the age of 30. That stone formation in the young females is equally common as in the males could partly depend on genetical factors. Thus, a considerably higher proportion of metabolic abnormalities of possible inherited origin has been found in young female stone formers than in male (Backman, 1976). It may be that in these women a predisposition for the formation of stones becomes of greater importance, whereas in the males other factors predominate, for example environmental ones, acting over several years.

For both sexes it appeared that recurrences were common (close to 50% after a mean observation period of ten years). Individuals with an early onset of stone disease were particularly prone to frequent recurrences and thus may constitute a group in which early clinical and metabolic investigations and attempts at prophylactic treatment are justified.

It is suggested from the present study that stone disease is becoming an increasing problem, already affecting a considerable number of individuals. It therefore seems desirable to disclose the possible dominating factor responsible for this development. Further studies with an epidemiologic design are thus warranted to elucidate the mechanisms behind the increasing incidence of renal stone disease.

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URINARY ELECTROLYTES IN RENAL STONE FORMERS AND HEALTHY SUBJECTS

A population study of 60-year-old men

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ABSTRACT

The 24-hour, urinary excretion of calcium, magnesium, phosphate, sodium and potassium was investigated in a population study of 331 60-year-old men participating in a general health survey. The prevalence of renal stone disease was 18.1%. Stone formers as a group had a significantly raised excretion of calcium (mean $\pm$ SD., 6.5 ± 3.5 mmol/24 h) compared with matched, healthy, control subjects (5.3 ± 2.8 mmol/24 h). The prevalence of renal stones was correlated to urinary calcium varying from 3.3% in the lowest to 26.7% in the highest percentile group of calcium excretion. Statistical analysis indicated that stone formers were not particularly accumulated in the upper part of the normal frequency distribution of urinary calcium but rather constituted a population with an excess excretion of calcium of approximately 20% over the whole range of values. Mean values and frequency distributions for the other electrolytes were not significantly different in renal stone formers, compared with the stone-free population. There was a positive correlation between urinary calcium and magnesium in both stone formers and healthy subjects but stone formers had a slightly lower magnesium output for any given level of urinary calcium. Irrespective of the calcium excretion, the subjects with a high, urinary, Ca/Mg ratio had a greater prevalence of stones than those with a low ratio. This study thus supports the view that a high rate of urinary calcium is a risk factor for common renal stone disease and also provides evidence for a protective effect of urinary magnesium.

INTRODUCTION

The quantitative investigation of urinary constituents has been a common procedure in the study of renal stone disease. A raised output of calcium in a large number of stone patients has long been regarded as a distinctive feature of idiopathic stone disease (Flocks, 1939; Albright, Henneman, Benedict & Forbes, 1953; Coe & Kavalach, 1974; Rose & Harrison, 1974). However, this view has not been uniformly supported and several recent reports question the importance of urinary calcium in stone formation (Garrido, Jimenez, Damiano & Orozco, 1973; Welshman & McGeown, 1975; Jørgensen, 1975). On the basis of different patterns of electrolyte excretions in stone formers compared with controls, other ions have also been presumed to be of importance in stone disease. Thus, it has been suggested that a reduced sodium (Modlin, 1967) or magnesium (Evans, Forbes, Sutton & Watson, 1967; Hodgkinson, 1974) output may be of significance in the pathogenesis of renal stones. The correct evaluation of all these aspects seem to be dependent on the selection of proper control materials. It is known that the excretion of calcium is influenced by age, sex and body weight (Bulusu, Hodgkinson, Nordin & Peacock, 1970; Davis, Morgan & Rivlin, 1970), and large seasonal variations have also been demonstrated (Morgan, Rivlin & Davis, 1972; Robertson, Gallagher, Marshall, Peacock & Nordin, 1974).

Although renal stones seem to occur frequently in the population (Ljunghall & Hedstrand, 1975; Ljunghall, Christensson & Wengle, 1977), few investigations with an epidemiological design have been performed. In the present study, urinary electrolytes were analyzed in individuals recruited from a general health survey. This provided the opportunity to obtain closely matched controls, increasing the possibility of detecting even small differences in the excretion patterns between stone formers and healthy subjects. A population study also makes it possible to estimate the prevalence of renal stones at various levels of the different electrolyte excretions, i.e. the "risk" of renal stones forming in relation to the urinary electrolytes. It was therefore hoped that information would be obtained as to when an alteration of the individual patient's electrolyte excretion may be of therapeutical importance.

MATERIAL

A general health survey, primarily focussed on risk factors for coronary heart disease, was offered all men born in 1915 and living in Uppsala (Waern, 1977). Altogether 331 individuals attended the investigation (participation rate 78.4%) which took place during the period August–November 1975. From this survey, the following groups were selected for the present study.

I. Renal stone formers

This group consisted of 60 subjects (18.1% of the population). The criteria for renal stone disease were essentially the same as those used in a previous study (Ljunghall & Hedstrand, 1975). In short they consisted of either a visualized stone (a) on X-ray, (b) at operation or (c) after spontaneous passage or (d) a clinical diagnosis made by a physician at the time of characteristic symptoms of renal colic. This last criterion (d) had to be applied only to nine subjects, eight of whom had experienced a single stone. In all but three of these cases, supporting records were available from the examining physician. No case had to be excluded because of a discrepancy between the patient's own history and that obtained from hospital or out-patient records. For the analysis of urinary electrolytes, only data from the 51 individuals were used who were considered healthy without any regular dietary or drug treatment of possible significance for electrolyte excretion.

II. Apparently healthy controls

Of the 271 stone-free participants, 16 were excluded because of dietary or drug treatment by the same criteria as those used in the case of stone formers. From the remaining 255, a matched control group was selected, in order to reduce possible seasonal or laboratory variations. This group of 51 subjects comprised one individual for each renal stone former. The matched controls had always been examined on the same day as the index person.

METHODS

All the participants were requested to collect all their urine for the 24 hours following the health survey. Four individuals, all belonging to the control group, refused to take part in this study. All the subjects were ambulant

with no restrictions on their ordinary diet, which, according to recalculations of data obtained in a previous study (Ljunghall & Hedstrand, 1976), generally provides around 1,000 mg of calcium per day in this area.

Urine was collected in plastic bottles without preservatives. After acidification with concentrated nitric acid, analyses were carried out by the current methods in use at the Department of Clinical Chemistry. Urinary calcium and magnesium were determined by atomic absorption, sodium and potassium by flame photometry, phosphate by a phosphomolybdic method and creatinine by a Jaffé method. The intra- and inter-day variations for all analyses were within 1-2% except for phosphate where determinations varied between 2-5%.

Calculations

In order to reduce the possible errors from inadequate urine collection, variations in the electrolyte excretion due to body size or differences in glomerular filtration rate values were related to the simultaneously obtained, 24-hour clearance of creatinine (C_{Cr}), using the formula of Nordin, Hodgkinson & Peacock (1967):

$$\begin{aligned} \text{Adjusted electrolyte excretion} &= \\ &= \frac{24\text{-hour excretion} \times \text{serum creatinine concentration}}{24\text{-hour creatinine excretion}} \end{aligned}$$

The tubular re-absorption of phosphate (TRP) was also derived from the 24-hour volume as

$$\text{TRP \%} = \left(1 - \frac{\text{Clearance of phosphate}}{C_{Cr}}\right) \times 100.$$

Statistical methods

For comparisons between stone formers and matched controls, Student's t-test was used on log values. The X^2 -test, for small populations with Yates's correction, was used for comparison of frequencies. Regression analysis was used to study associations between urinary electrolytes. All these methods can be found in Armitage (1971).

Table I. Total number of renal stones in relation to age at onset of stone disease in a health survey of 60-year-old men

Age at onset (years)	No of stones				No of patients	
	1	2-3	4-9	10-	n	%
- 24					0	0
25 - 29	1			1	2	3.3
30 - 34	2	2	1	1	6	10.0
35 - 39	5	3	1	4	13	21.7
40 - 44	3	3	1		7	11.7
45 - 49	6	4			10	16.7
50 - 54	8	6	1		15	25.0
55 - 59	6	1			7	11.7
Total no of patients	31	19	4	6	60	100.0

RESULTS

Prevalence of renal stones

Among the 331 participants in the health survey, 60 (18.1%) had a history of renal stones. Thirty-three of the 92 non-participants answered a postal enquiry. Six of them (18.2%) had experienced renal stones. Table I shows the total number of stones in relation to age at the onset of stone disease. In Figure 1, the five-year incidence of stones is illustrated and compared with the results previously obtained in a group of individuals ten years younger from a previous population study (Ljunghall & Hedstrand, 1975).

Table II summarizes some clinical and biochemical findings. No significant differences were obtained between stone formers and healthy subjects, nor were there any differences between single or recurrent stone formers. No case of hypercalcaemia was detected and no individual in the entire age-group had previously been operated upon for hyperparathyroidism.

The following analysis of urinary electrolytes in stone formers deals only with those 51 (16.9% of the population) who were otherwise apparently healthy.

Table II. Some clinical and biochemical findings (mean $\pm$ S.D.) in renal stone formers (n = 51) and matched controls from a health survey of 60-year-old men

	Renal stone formers	Controls
Serum calcium, mmol/l	2.41 $\pm$ 0.07	2.41 $\pm$ 0.08
Serum phosphate, mmol/l	0.91 $\pm$ 0.12	0.95 $\pm$ 0.28
Serum uric acid, μ mol/l	258 $\pm$ 54	269 $\pm$ 66
Serum creatinine, μ mol/l	81 $\pm$ 10	83 $\pm$ 14
24-hour creatinine clearance, ml/min	94 $\pm$ 21	91 $\pm$ 23
24-hour tubular re-absorption of phosphate, %	97.7 $\pm$ 0.5	97.8 $\pm$ 0.7
Urinary volume, l/24 hour	1.230 $\pm$ 0.4	1.200 $\pm$ 0.4
Body weight, kg	77.4 $\pm$ 9.5	77.1 $\pm$ 11.1

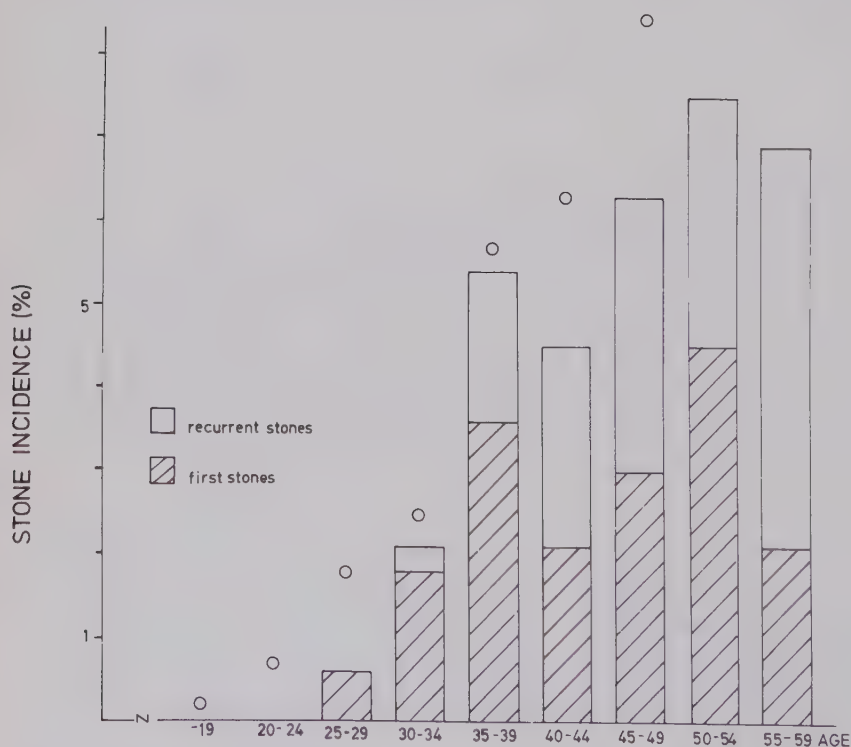


Figure 1. The incidence of renal stones per five-year period in a general health survey of 60-year-old men. The circles represent the corresponding incidence obtained from a population ten years younger (Ljunghall & Hedstrand, 1975). No subject is included more than once during each period.

Table III. The 24-hour, urinary, creatinine and electrolyte excretions (mean $\pm$ S.D.) in renal stone formers and apparently healthy subjects from a health survey of 60-year-old men

24-hour excretion (mmol)	Stone formers					Healthy subjects (n = 251)
	All (n = 51)	Single stones (n = 27)	Recurrent stones (n = 24)	Stones during last 5 years (n = 20)		
Calcium	6.5 $\pm$ 3.5 ^{xx}	6.2 $\pm$ 2.4 ^x	6.9 $\pm$ 4.4 ^x	7.4 $\pm$ 4.5 ^x		5.3 $\pm$ 2.8
Magnesium	3.7 $\pm$ 1.5	3.8 $\pm$ 1.7	3.6 $\pm$ 1.2	3.6 $\pm$ 1.4		3.8 $\pm$ 2.5
Potassium	69 $\pm$ 24	63 $\pm$ 19	76 $\pm$ 25	75 $\pm$ 31		70 $\pm$ 24
Sodium	162 $\pm$ 67	148 $\pm$ 47	177 $\pm$ 82	157 $\pm$ 59		155 $\pm$ 60
Phosphate	30 $\pm$ 7	31 $\pm$ 6	30 $\pm$ 7	31 $\pm$ 8		29 $\pm$ 8
Creatinine	16 $\pm$ 3	15 $\pm$ 3	16 $\pm$ 3	16 $\pm$ 4		15 $\pm$ 4

x) p < 0.05 when compared with matched controls

xx) p < 0.01 when compared with matched controls

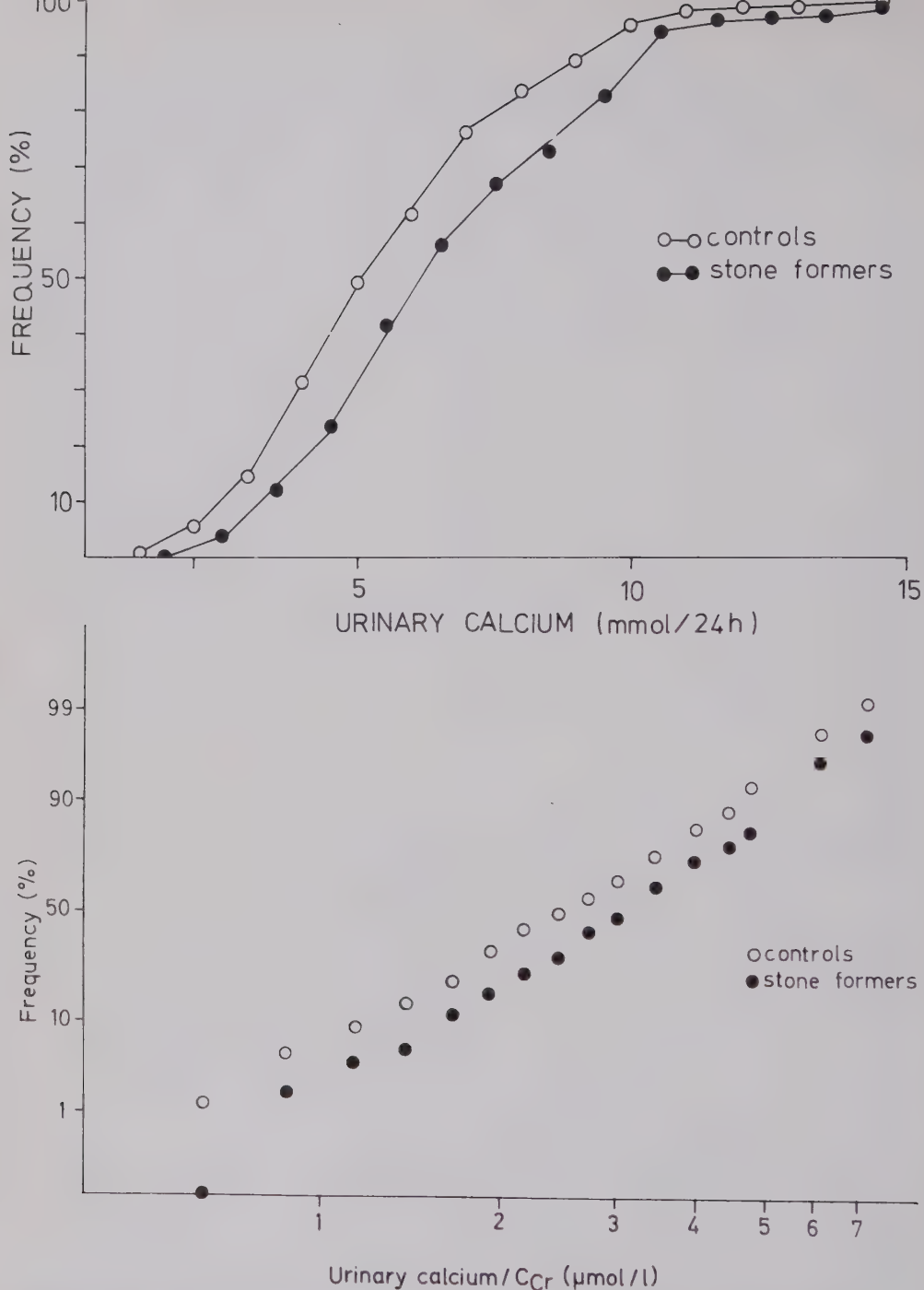


Figure 2. The cumulative frequency of the 24 hour, urinary, calcium excretion in renal stone formers ($n = 51$) and healthy subjects ($n = 251$) from a health survey of 60-year-old men. (Above) Absolute values for urinary calcium. (Below) Probit transformation of the frequency-distribution curves, adjusted for differences in the simultaneously obtained, creatinine clearance and expressed on a log scale.

Urinary electrolytes

Mean values for the urinary excretion of calcium, magnesium, phosphate, sodium, and potassium are shown in Table III. Only for urinary calcium were there any significant differences in the 24-hour excretions between stone formers and matched controls, whereas for the other electrolytes the mean values and frequency distributions were similar. There were no significant differences between the subgroups of stone formers for any of the parameters in the table. No further information was obtained when the excretion values were related to the simultaneously obtained C_{Cr} .

Frequency distribution of urinary calcium

Figure 2 shows the distribution curves for urinary calcium in stone formers and healthy subjects. Probit transformation (a change of the scale of the vertical axis such that a normal distribution will appear as a straight line) yielded a linear course over the greater part of the cumulative frequency-distribution curves but with slight distortions at the lower end for both groups. With a log scale on the horizontal axis, there was a linear distribution of values over the whole range of urinary calcium (Figure 2 b). This indicates that the underlying distributions were slightly skewed to the right, i.e. with an over-representation of high values in both stone formers and healthy subjects. Furthermore, probit transformation revealed that the distributions of urinary calcium in stone formers and in controls were shifted in relation to each other, i.e. the interval between the lines in Figure 2 b was constant over the whole range. The difference could be calculated from the means of log values as

$$\left(\frac{3.88 - 3.29}{3.29} \right) \times 100 = 18\%.$$

Inter-relations between urinary electrolytes

A raised excretion of any of the electrolytes was generally also associated with an increased output of all the other ions, i.e. there were positive correlations between the urinary electrolytes (Table IV). By calculating the partial correlation coefficients, it could not be demonstrated that any particular electrolyte was a major determinant of this pattern. There were no significant differences between the r-values when stone formers were compared with healthy subjects. Furthermore, when the regression equations for the rela-

Table IV. Correlation coefficients (r-values) between the 24-hour, urinary, electrolyte excretions (log values) in renal stone formers (A, n = 51) and healthy subjects (B, n = 251) from a health survey of 60-year-old men

Urinary electrolyte		Magnesium	Phosphate	Sodium	Potassium
Calcium	A	0.55 ^{xxx}	0.43 ^{xx}	0.42 ^{xx}	0.31 ^x
	B	0.37 ^{xxx}	0.35 ^{xxx}	0.12	0.15 ^x
Magnesium	A		0.36 ^{xx}	0.07	0.39 ^{xx}
	B		0.36 ^{xxx}	0.19 ^{xx}	0.24 ^{xxx}
Phosphate	A			0.25	0.41 ^{xx}
	B			0.28 ^{xxx}	0.47 ^{xxx}
Sodium	A				0.34 ^x
	B				0.43 ^{xxx}

x) p < 0.05
 xx) p < 0.01
 xxx) p < 0.001

tionships in Table IV were calculated, it was found that none of the regression coefficients, i.e. the slopes of the regression lines, was significantly different in the two groups. Also the intervals between these lines were analyzed. A significant difference could only be demonstrated for the relationship between calcium and magnesium. This is shown in Figure 3, where it will be seen that stone formers as a group had a lower magnesium output for any level of urinary calcium, i.e. the regression line was displaced downwards.

Prevalence of renal stones in relation to urinary electrolytes

The prevalence of stones in relation to the excretion of electrolytes is shown in Table V. There was a positive relationship between urinary calcium and the prevalence of stones, whereas no clear-cut pattern appeared for the other ions. There was, however, a suggestion of an inverse relationship among

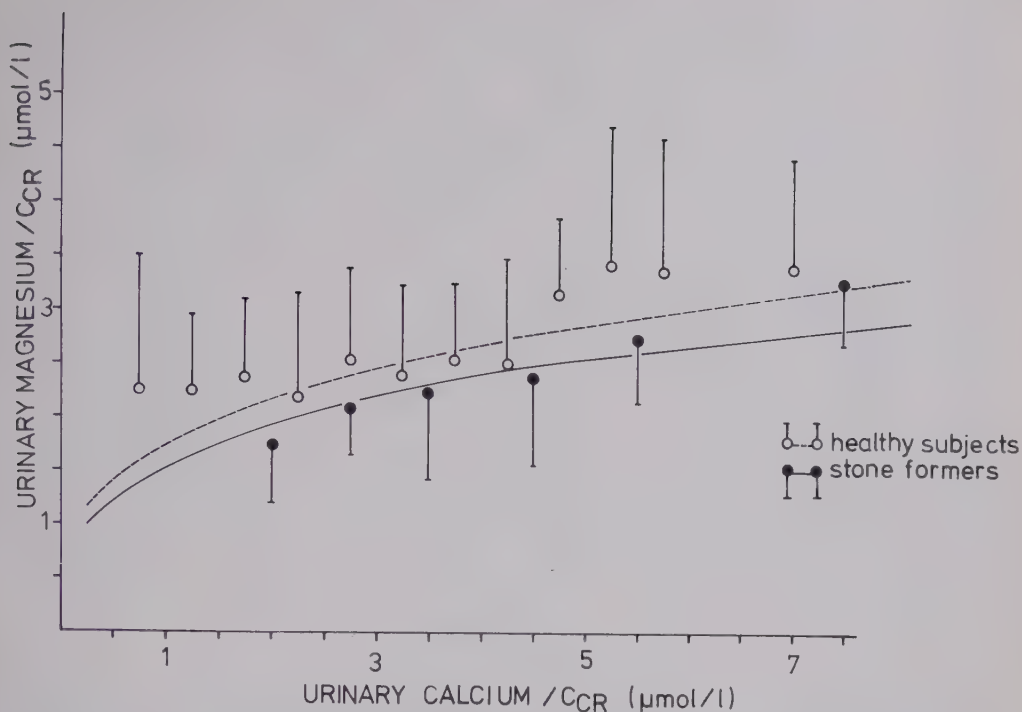


Figure 3. The relationship between urinary calcium and magnesium in renal stone formers ($n = 51$) and healthy subjects ($n = 251$) from a health survey of 60-year-old men. Symbols indicate mean ($\pm$ S.D.) of urinary magnesium for each $\mu\text{mol/l}$ of urinary calcium/ C_{CR} , except for the highest value, which is the sum of all values above 6 $\mu\text{mol/l}$. Stone formers are divided into groups of 8 or 9 subjects according to increasing, urinary, calcium values. The lines indicate the regression equations derived from log values (stone formers: $y = 2.81 x^{0.31}$, $r = 0.55$, $p < 0.001$; healthy subjects: $y = 2.49 x^{0.31}$, $r = 0.37$, $p < 0.001$).

those with the highest values for magnesium and potassium, despite the fact that these subjects also had higher-than-average urinary calcium. In the further analysis, therefore, the ratios between calcium and the other ions were calculated. Table VI shows that stone formers had higher ratios between urinary calcium and all other electrolytes. An increased ratio was also invariably associated with a greater prevalence of stones (Table VII). In most instances, however, this correlation was greatly dependent on the urinary calcium per se. Only for the relationship between calcium and magnesium did it appear that, even when individuals with identical calcium outputs were compared, a higher ratio was associated with a greater prevalence of stones (Table VIII). No such independent relationship could be demonstrated for any of the other electrolytes.

Table V. Prevalence of renal stone disease in a population study of 60-year-old men in relation to the percentile values for the 24-hour, urinary, electrolyte excretions, adjusted for differences in creatinine clearance

Percentiles of electrolyte excretion	No of subjects	Prevalence of stone disease (%) within each percentile group				
		Calcium	Magnesium	Phosphate	Sodium	Potassium
0 - 10	30	3.3	20.0	10.0	20.0	20.0
10 - 25	45	11.1	24.4	17.8	17.8	24.4
25 - 50	76	18.4	15.8	21.1	15.8	17.1
50 - 75	76	18.4	14.5	11.8	17.1	14.5
75 - 90	45	20.0	17.8	20.0	17.8	15.6
90 - 100	30	26.7	10.0	20.0	13.3	10.0
0 - 100	302	16.9	16.9	16.9	16.9	16.9

Table VI. Ratios of 24-hour, urinary, electrolyte excretions (mean $\pm$ S.D.) in renal stone formers (n = 51) and matched controls from a health survey of 60-year-old men

Ratio (mmol/mmol)	Stone formers	Controls
Calcium/ Magnesium	1.98 $\pm$ 1.57 ^{xx}	1.61 $\pm$ 1.46
Calcium/ Phosphate	0.22 $\pm$ 0.15 ^{xx}	0.19 $\pm$ 0.10
Calcium/ Sodium	0.043 $\pm$ 0.021 ^{xx}	0.041 $\pm$ 0.05
Calcium/ Potassium	0.099 $\pm$ 0.048 ^{xx}	0.083 $\pm$ 0.045

xx) p < 0.01

DISCUSSION

In this study from a general health survey of 60-year-old men, there was a prevalence of renal stones of 18.1%. There was no tendency to a decrease in stone incidence with time before the age of 60. Hence, the biochemical findings may also be valid for younger stone formers. A previous study of a population born five to ten years later showed a corresponding prevalence of 13.7%. In the younger population, stone disease started at an earlier age and more individuals were affected when subjects of roughly the same age were compared. These observations agree with the results obtained in a larger population study (Ljunghall, Christensson & Wengle, 1977).

The advantages of an epidemiological study were obtained at the expense of certain drawbacks. It was not possible in every instance to get an absolutely definite diagnosis of stones and a few cases had to be included only on the basis of a characteristic clinical picture. When their biochemical pattern was analyzed separately, no deviation from that of verified stone formers appeared. Furthermore, in some instances, the 24-hour, urine collections may have been inadequate. When corrections were made for the simultaneously obtained C_{Cr} , only minor effects on the frequency-distribution curves were found, suggesting that, as a rule, the urine collections had been fairly accurate. As the study was primarily concerned with comparisons between stone formers

Table VII. Prevalence of renal stones in relation to the ratios of urinary electrolytes expressed as percentile values

Percentiles of ratios	No of subjects	Stone prevalence (%) within each percentile group			
		Ca/Mg	Ca/P	Ca/Na	Ca/K
0 - 10	30	0	6.3	13.1	6.1
10 - 25	45	9.1	17.2	8.5	7.7
25 - 50	76	15.0	14.8	18.1	17.3
50 - 75	76	25.5	18.1	17.4	14.1
75 - 90	45	26.4	22.4	24.4	24.6
90 - 100	30	25.8	21.1	21.2	27.3
0 - 100	302	16.9	16.9	16.9	16.9

Table VIII. Prevalence of renal stones in relation to the Ca/Mg ratio and the 24-hour urinary calcium excretion

Urinary calcium/ C_{Cr} ($\mu\text{mol/l}$)	$\text{Ca/Mg} \leq 1.5 \text{ mmol/mmol}$		$\text{Ca/Mg} > 1.5 \text{ mmol/mmol}$		Significance of difference
	No of subjects	Stone pre- valence, %	No of subjects	Stone pre- valence, %	
- 2.9	98	13.3	23	13.0	ns
3.0 - 3.9	27	14.8	32	18.8	ns
4.0 - 4.9	22	4.5	36	25.0	$p < 0.05$
5.0 -	16	0	48	31.3	$p < 0.01$
All values	163	11.0	139	23.7	$p < 0.01$

and healthy subjects and as the total creatinine excretions was almost identical in the different groups, this comparative analysis was probably not invalidated by systematic errors in urine collections.

Stone formers as a group had a raised excretion of calcium, whatever the mode of its expression, in absolute amounts, in relation to C_{Cr} , body weight or urinary volume. The probit transformation of the cumulative frequency distributions indicated that stone formers were not simply accumulated in the upper part of the normal range but, compared with stone-free subjects, constituted a different population with a general excess excretion of calcium of approximately 20%. Statistical analysis further indicated that the distributions were similar in the two groups, with a slight skewing to the right. This contrasts with the results of Robertson & Morgan (1972), who, without performing a log transformation before probit transformation, obtained a distortion at the lower end of the curve and therefore suggested that stone formers were unable to excrete small amounts of calcium. However, it has been shown that, when the gastro-intestinal calcium absorption is diminished, stone formers can reduce their calcium outputs to levels probably closely similar to those of healthy subjects also in the lower region of values (Keynes, Barnes & Cope, 1971; Pietrik & Kokot, 1973; Pak, Delea & Bartter, 1974).

In the entire population, the mean, daily, calcium excretion was 5.4 mmol. With the common criteria of mean value + 2 S.D., the upper limit of the normal range would be 11 mmol. In that case, only 6% of all stone formers could actually be regarded as hypercalcurics. With the widely accepted limit of 7.5 mmol (Hodgkinson & Pyrah, 1958), 35% of all stone formers and also 20% of the stone-free population would be classified as having an abnormal calcium output. Since most stone formers could rather be considered to have a relative hypercalciuria of about 20% there appear to be no certain advantages in the use of an arbitrary upper limit for urinary calcium, at least not in the sense of its constituting a watershed in the selection of prophylactic therapy. In the present study, which could provide an estimate of the association between urinary electrolytes and renal stones, since it was concerned with a representative sample of the population, stone disease was correlated to calcium excretion over the whole range of values and stones were rare only among those in the very lowest part of the frequency distribution. This further indicates that it is probably important to reduce calcium excretion also in those stone formers who have values well within the normal range, as well as

in those with hypercalciuria in the strictest sense. The association between urinary calcium and stone prevalence, together with previous reports of the beneficial effect of a reduction in calcium output on stone disease (Yendt & Cohanim, 1973; Pak et al, 1974) strongly supports the appropriateness of considering a high value of urinary calcium as a risk factor for renal stone formation.

Positive correlations were generally obtained between all electrolytes, both in stone formers and in healthy subjects. This pattern is probably the result of complex interactions between various dietary factors promoting a general hyperabsorption (Lindeman, Adler, Yiengst & Beard, 1967), electrolyte intake (Barker, Elkinton & Clark, 1959; Hills, Parsons, Webster Jr, Rosenthal & Conover, 1959; Clark, Charles & Rivera-Cordero, 1965; Dunn & Walser, 1966) and interdependent transport mechanisms in the kidney (Walser, 1961a; Vander, 1961; Malnic, Klose & Giebisch, 1966; Duarte & Watson, 1967; Massry, Ahumada, Coburn & Kleeman, 1967). In spite of these positive associations, which were similar in stone formers and controls, no other electrolyte showed a consistent relationship to renal stone disease comparable to that of urinary calcium.

It has been recognized for a long time that in vitro magnesium increases the solubility of calcium oxalate (Hammarsten, 1929), the most common constituent of renal stones, and therapy with magnesium salts has been effective in cases of recurrent stone disease (Gershoff & Prien, 1967; Silver & Brendler, 1971; Melnick, Landes, Hoffman & Burch, 1971). A low excretion of magnesium has been reported in stone formers (Evans et al, 1967; Hodgkinson, 1974) but has not been definitely confirmed (Jørgensen, 1975; Welshman & McGeown, 1975). Thus, the role of magnesium in renal stone disease is not clearly established. Some studies argue that the ratio between calcium and magnesium rather than the absolute amounts of these two substances is of greatest importance (King Jr, O'Connor jr, Smith & Crouse, 1968; Oreopoulos, Soyannwo & McGeown, 1968; Jørgensen, 1975; Welshman & McGeown, 1975). From these reports, it has not always been possible to conclude whether an increased Ca/Mg ratio depended on an increase in calcium, a decrease in magnesium or perhaps both factors at the same time. In the present study, the value of urinary magnesium in stone formers was close to that of healthy subjects without any accumulation of low ones. The increased Ca/Mg ratio in stone formers was thus primarily due to the increased urinary calcium. The relationship between the two ions was, however, set at a

different level in stone formers with a lower magnesium output for any calcium value over the whole range. Furthermore, the increased prevalence of stones in subjects with a high Ca/Mg ratio could not be explained solely by the raised calcium, since it was apparent also when individuals with identical calcium outputs were compared. These findings indicate that urinary magnesium plays a protective role against the formation of renal stones and suggest that a disturbance of the relationship between calcium and magnesium may be of importance for lithogenesis.

The hypothesis that urinary sodium is an important protective factor against the development of renal stones has been put forward by Modlin (1967). This was unexpected, in view of the fact that sodium and calcium excretions are closely linked (Walser, 1961b; Klemann, Bohannon, Bernstein, Ling & Maxwell, 1964). Most later reports have not supported his findings (Philips & Cooke, 1967; Fogarthy, 1971; Jørgensen, 1975) and the present study does not provide any evidence of an inhibitory role of sodium excretion in stone formation.

Low serum concentrations of inorganic phosphate have long been recognized as a hall-mark of "idiopathic hypercalciuria" (Albright et al, 1953; Henne-man, Benedict, Forbes & Dudley, 1958). This relationship is also confirmed in some recent reports (Gray, Caldas, Wilz & Lemann, 1976; Shen, Baylink, Nielsen, Sherrard & Haussler, 1976) but not invariably so (Jørgensen, 1975). In the present study, a low serum phosphate level was not a typical feature of stone formers, nor were there any differences in the renal excretion or tubular handling on a 24-hour basis. This is in agreement with our previous population study (Ljunghall, Hedstrand, Hellsing & Wibell, 1977). It may be that the importance of a low serum phosphate is apparent primarily in patients investigated because of a more complicated stone disease than among unselected stone formers from a health survey.

There were no significant differences in the patterns of electrolyte excretion between subgroups of patients divided according to the number of stones or the time since the last passage of stones. Although several factors other than urinary electrolytes are of importance for the development of renal stones (Nordin, 1973) this lack of difference between single and recurrent stone formers is in accordance with the observation that the risk of recurrence persists for a long time after the first stone incident (Williams, 1963; Ljunghall & Hedstrand, 1975). Thus, it seems as if stone formers have a certain risk-

factor profile, more or less pronounced, upon which other stone-promoting factors are super-imposed. If the excretion pattern in stone-free subjects is accepted as the therapeutical guideline, the present study indicates that a reduction of the urinary calcium of about 20%, possibly together with an increased output of magnesium, would be of benefit in prophylaxis against recurrence.

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MECHANISMS OF HYPERCALCIURIA IN RECURRENT RENAL STONE FORMERS

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ABSTRACT

Hypercalciuria, which is frequently encountered in cases of the recurrent formation of renal stones, may theoretically be due to intestinal calcium hyperabsorption, increased bone resorption or inefficient, renal tubular re-absorption, either alone or in combination. In the present study, 34 recurrent renal stone formers with repeatedly normal serum calcium concentrations were investigated. The fractional, gastro-intestinal calcium absorption (F_{Ca}) was determined by an isotope technique. The urinary excretions of calcium and cyclic AMP (cAMP) were measured during a 24-hour period, in the fasting state and after an oral calcium load. Tests were also made of the renal acidifying capacity, as well as determinations of the urinary excretion of beta-2-microglobulin and hydroxyproline.

Compared with healthy controls, the renal stone formers had a raised F_{Ca} , which was correlated to the 24-hour urine calcium. The urinary cAMP was not different in stone formers and controls and was on the whole, inversely related to the urinary calcium output. Also the fasting urinary calcium was elevated in stone formers, suggesting an increased bone resorption, although the urinary excretion of hydroxyproline was not different from controls. In nine of the stone patients, there was evidence of an impaired renal tubular function. This group did not differ significantly from the other stone formers as regarded the urinary excretion of calcium or cAMP.

This study indicates that gastro-intestinal calcium hyperabsorption, possibly in some individuals together with an increased bone resorption, is the major source of the raised urinary calcium in recurrent renal stone formers. The results are compatible with the concept of a fundamental disturbance of the calcium metabolism in these patients, leading to a high calcium turnover. In normocalcemic individuals this pattern is apparently not generally caused by parathyroid hyperfunction.

INTRODUCTION

Patients with recurrent renal stones often have a high urinary excretion of calcium (Nordin, Peacock & Marshall, 1976). The term "idiopathic hypercalciuria" is used for a syndrome characterized by normocalcemia and hypercalciuria that is unexplained by an established cause, such as sarcoidosis or immobilization (Albright, Henneman, Benedict & Forbes, 1953; Henneman, Benedict, Forbes & Dudley, 1958). Kidney stones are common and in the original reports a tendency towards hypophosphatemia was also a common feature. In this group of patients, a gastro-intestinal hyperabsorption of calcium is commonly present (Nordin et al, 1976). There are divergent opinions as to whether the raised absorption is a primary phenomenon (Nordin, Hodgkinson & Peacock, 1972), secondary to a renal tubular defect in calcium reabsorption (Coe, Canterbury, Firpo & Reiss, 1973) or part of the picture of hyperparathyroidism (HPT) also in individuals with apparently normal serum calcium levels (Muldowney, Freaney, McMullin, Towers, Spillane, O'Connor, O'Donohoe & Moloney, 1976). The limit for the definition of hypercalciuria is generally arbitrarily chosen and usually varies between 6 and 10 mmol/24 hours (Hodgkinson & Pyrah, 1958; Davis, Morgan & Rivlin, 1970). A previous population study (Ljunghall & Waern, 1977) indicated that stone formers were not particularly accumulated in the upper part of the normal frequency distribution of urinary calcium. It rather appeared that the stone-forming and stone-free groups were shifted in relation to each other, stone formers having an excretion of calcium raised by approximately 20% compared with the matched controls. In the present report, therefore, this over-excretion of calcium has been denoted by the term "hypercalciuria" although in most instances stone formers did not have a calcium output exceeding the mean + 2 S.D. value obtained in healthy controls. Among patients with recurrent renal stones, 5-10% have hypercalcemia, usually due to HPT (Lavan, Neale & Posen, 1971; Coe & Kavalach, 1974; Ljunghall, Hedstrand, Hellsing & Wibell, 1977). The present study only included individuals with serum calcium values within the normal limits and was undertaken to evaluate the relative importance of the different possible mechanisms responsible for the raised, urinary calcium excretion in recurrent renal stone formers.

MATERIAL

Stone patients

This study presents data obtained from 34 consecutive patients (8 women, 26 men) referred to an out-patient, kidney-stone clinic for the evaluation of recurrent renal stone disease. All the patients had passed calcium-containing stones during the year before the study. Their mean age was 42 years (range 23-65 years). Only patients who were otherwise apparently healthy, without prior neck exploration and were undergoing no dietary or drug treatment were included. Their stone disease had lasted for an average of eight years (range 3-23 years) and a mean of eight stones had been passed (range 3-50). Pyelolithotomies had been performed in six patients, but in no case had any significant amount of renal tissue been excised. Intravenous pyelograms were normal in all of them except for residual stones in a few instances. All the patients had repeatedly normal serum calcium (mean 2.43 ± 0.05 (S.D.) mmol/l, range 2.35 - 2.54 mmol/l) and phosphate values (mean 0.91 ± 0.15 mmol/l, range 0.70 - 1.30 mmol/l). Normal values were also obtained in all cases for serum alkaline phosphatase, uric acid and creatinine. No patient had albuminuria or a positive urine culture and all had a negative test for cystinuria (Brand's test). The patients were all ambulants receiving their ordinary diet.

Hyperparathyroidism (HPT) patients

For comparison, some data are also presented from a group of 14 patients with operatively verified, parathyroid adenomas, studied immediately prior to and also, in all cases but one, three months after operation. This group consisted of five men and nine women aged between 27 and 73 (mean age 57 years), six of them with a past or present history of renal stones. All the patients had normal serum creatinine and alkaline phosphatase concentrations.

Controls

Isotope studies of the gastro-intestinal calcium absorption and measurements of the urinary calcium excretion were performed on 15 male medical students and members of the staff. In 10 of these and in 10 female students, determinations were also made of the urinary excretion of cyclic AMP. All the control

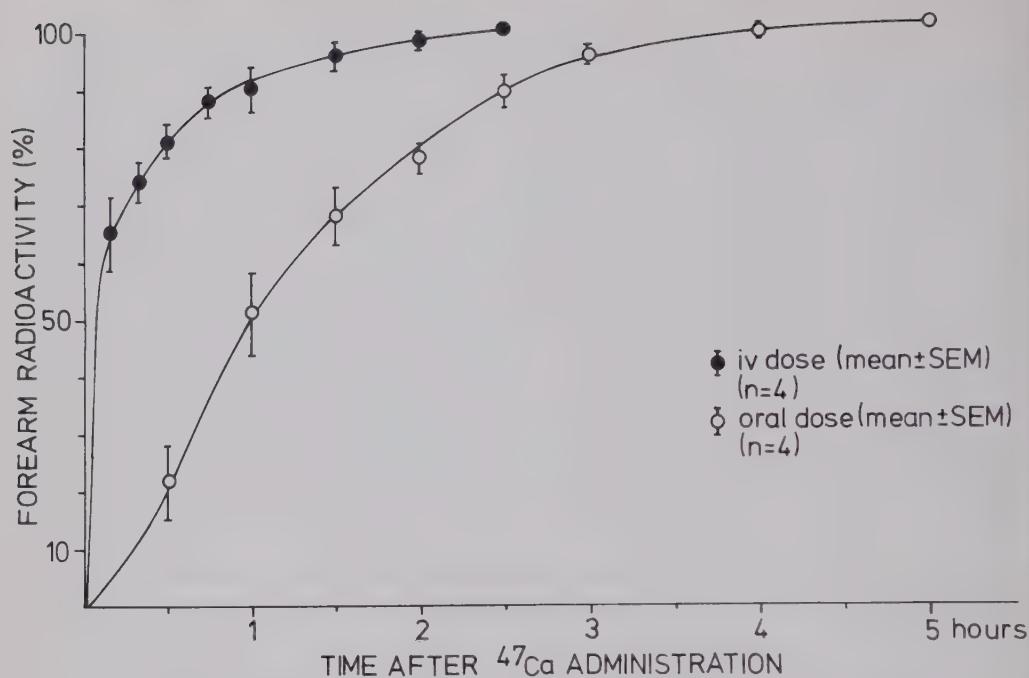


Figure 1. Forearm radioactivity in four healthy subjects after oral and intravenous administrations of ^{47}Ca .

individuals were apparently healthy, with no histories of renal stones. Their mean age was 31 years (range 23–41 years).

METHODS

The gastro-intestinal absorption of calcium was estimated by a technique modified from Wills, Zisman, Wortsman, Evens, Pak & Bartter (1970). The method is based on the external measurement of ^{47}Ca in the forearm after intravenous (i.v.) and oral administration of the radionuclide.

Pilot experiments established that the forearm activity reached a plateau within 2 hours after the i.v. dose and within 6 hours after the oral dose (Figure 1), decay from that time onwards being exponential. The measurements were always performed after these times intervals and in the majority of the cases 20 hours after the i.v. administration and 24 hours after the oral one.

The administrations were made with an interval of two days and in random order. The i.v. radio-active dose was 1-2 μCi $^{47}\text{CaCl}_2$ (Radiochemical Centre, Amersham, U.K.) and the peroral 5-10 μCi . The latter was given together with 200 mg $^{40}\text{CaCl}_2$ (equivalent to 65 mg Ca). The subjects had fasted for at least 12 hours before the oral dose and continued fasting for 4 hours after it. A lead chamber with walls 5 cm thick and with two 2" x 3" NaI (Tl) detectors in apposition was used in the measurements. A pulse-height window corresponding to photon energies between 0.6 - 1.6 MeV was used and counts were recorded for 200 seconds. The measurements yielded the fractional gastro-intestinal absorption of calcium (F_{Ca}), estimated as the ratio between the forearm count rates (corrected for background and administered radio-activity) after oral and i.v. administration, respectively.

The reproducibility of the method was tested in six healthy subjects, who were studied twice with at least one month's interval. The mean values of F_{Ca} in these individuals were $55 \pm 7\%$ (S.D.) and $54 \pm 11\%$, respectively. The mean individual difference between the two measurements was $7 \pm 4\%$ (range 1-11%) and the correlation coefficient between the two determinations 0.96.

Fasting urinary calcium and oral calcium load was performed as a six-hour study after overnight fasting. At the start of the test, the subjects drank 500 ml of distilled water, after which urine was collected for the following 2 hours. After renewed bladder-emptying 1 g of calcium (Calcium-Sandoz^R) was given, together with 500 ml of tap-water. Urine was then collected for another 4 hours. The subjects remained fasting throughout the test. Urines from the two collection periods were analyzed for calcium and cAMP, and in some instances, hydroxyproline. All values were expressed in relation to the urinary creatinine.

A short-term ammonium chloride loading was performed according to Backman, Danielson & Sohtell (1976).

Urinary cyclic AMP (cAMP) was measured by a radio-immuno-assay technique (Schwartz & Mann, Orangeburg, New York). The coefficient of variation was 8% and the reference range obtained from healthy subjects (mean $\pm$ 2 S.D.) 0.6 - 5.4 $\mu\text{mol/g}$ creatinine (Wålinder, Ljunghall & Wibell, 1977).

Venous blood samples were obtained in the morning after overnight fasting.

Table I. Fractional gastro-intestinal calcium absorption (F_{Ca}) and urinary calcium excretion in a 24-hour collection, after a 12-hour fast and after an oral calcium load in renal stone formers ($n = 34$) and controls ($n = 15$). (Mean values $\pm$ S.D.)

	F_{Ca} (%)	Urinary calcium		
		mmol/24 h	Fasting (mmol/mmol creat)	After calcium load (mmol/mmol creat)
Stone formers	72 ± 15	8.4 ± 2.0	0.34 ± 0.14	0.61 ± 0.18
Controls	60 ± 17	6.4 ± 1.6	0.25 ± 0.13	0.44 ± 0.16
Significance of difference	$p < 0.05$	$p < 0.001$	$p < 0.05$	$p < 0.01$

Table II. Urinary excretion of cyclic AMP (cAMP) in a 24-hour collection, after a 12-hour fast and after an oral calcium load in renal stone formers ($n = 34$) and controls ($n = 20$). (Mean values $\pm$ S.D.)

	Urinary cAMP (μ mol/g creat)		
	24 hour collection	Fasting	After calcium load
Stone formers	3.0 ± 1.3	3.6 ± 1.2	2.9 ± 1.3
Controls	3.5 ± 0.9	3.7 ± 1.1	3.0 ± 1.0
Significance of difference	-	-	-

Serum and urinary calcium concentrations were determined by atomic absorption. The normal range for the serum calcium concentration in our laboratory is 2.20 - 2.60 mmol/l.

Serum phosphate concentrations were determined by a phospho-molybdic method (reference range 0.76 - 1.44 mmol/l).

The 24-hour, urinary excretion of beta-2-microglobulin was analyzed by a radio-immuno-assay technique (Phadebas^R, Pharmacia Diagnostics, Uppsala, Sweden). An upper limit of the normal of 370 µg/24 hours was applied.

Urinary hydroxyproline excretion was determined by a colorimetric method (Hyperonosticon^R, Organon, Oss, Netherlands) in urine specimens obtained after a 12-hour fast. No dietary restrictions were instituted. The coefficient of variation was 12%.

Conventional statistical methods were applied (Armitage, 1971).

RESULTS

Calcium absorption and excretion: Urinary cAMP

Renal stone formers had a raised, fractional, calcium absorption (F_{Ca}) and a greater excretion of calcium in a 24-hour collection, in the fasting state and after an oral calcium load, compared with control subjects (Table I). No differences were obtained for the urinary excretion of cAMP between the two groups during the same collection periods (Table II). In stone formers, the 24-hour urine calcium was correlated to F_{Ca} (Figure 2). This was primarily due to the fact that all patients with F_{Ca} above 70% had a urinary calcium excretion of at least 7.5 mmol/24 hours, whereas no correlation was obtained for lower values of F_{Ca} and calcium output, either in stone formers or in controls.

Relationship between urinary calcium and cAMP excretions

There was an inverse relationship between the 24-hour urinary excretions of calcium and cAMP (Figure 3). Compared with the HPT patients in our previous study (Wålinder et al, 1977) the urinary cAMP in stone formers was lower

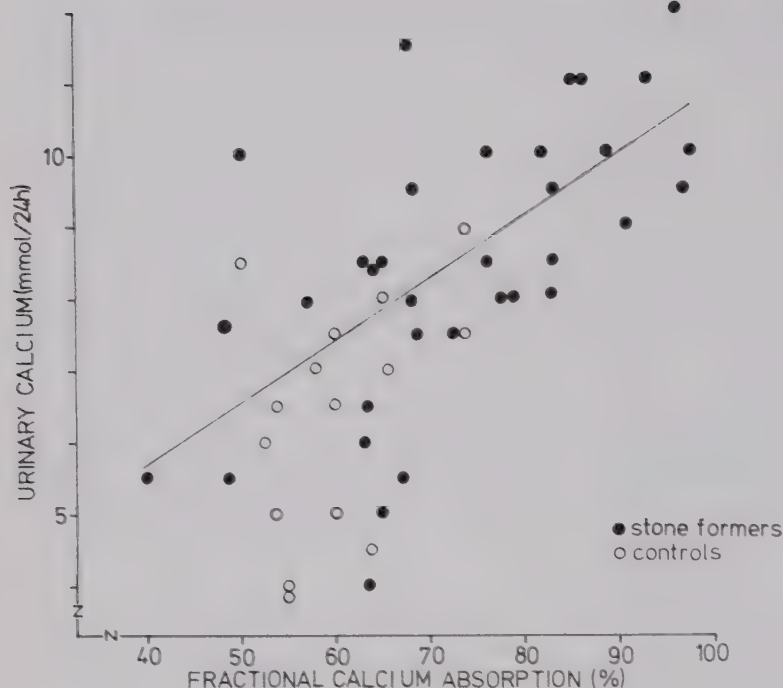


Figure 2. The relationship between the fractional gastro-intestinal calcium absorption and the 24-hour urine calcium in renal stone formers and controls. The regression line for the stone formers is indicated ($r = 0.61$, $p < 0.001$).

throughout the range for urinary calcium. The regression equations for stone formers and controls were closely similar. Thus, at comparable calcium excretions, no differences could be detected between the two groups and the urinary cAMP in stone formers was in all cases within 2 S.D. of the values from controls. A similar relationship was also obtained for the fasting, urinary excretions of calcium and cAMP (Figure 4).

Fasting urinary calcium and hydroxyproline excretions

The fasting, urinary calcium was significantly raised in stone formers (Table I). Both in stone formers and in controls, there was a positive correlation between the excretions of calcium in the fasting state and those collected during a 24-hour period (Figure 5). The regression equations for the two groups were not significantly different. In five stone formers, the fasting urinary calcium was raised above the upper limit (mean + 2 S.D.) obtained from controls. All these individuals had 24-hour, urine calcium values above

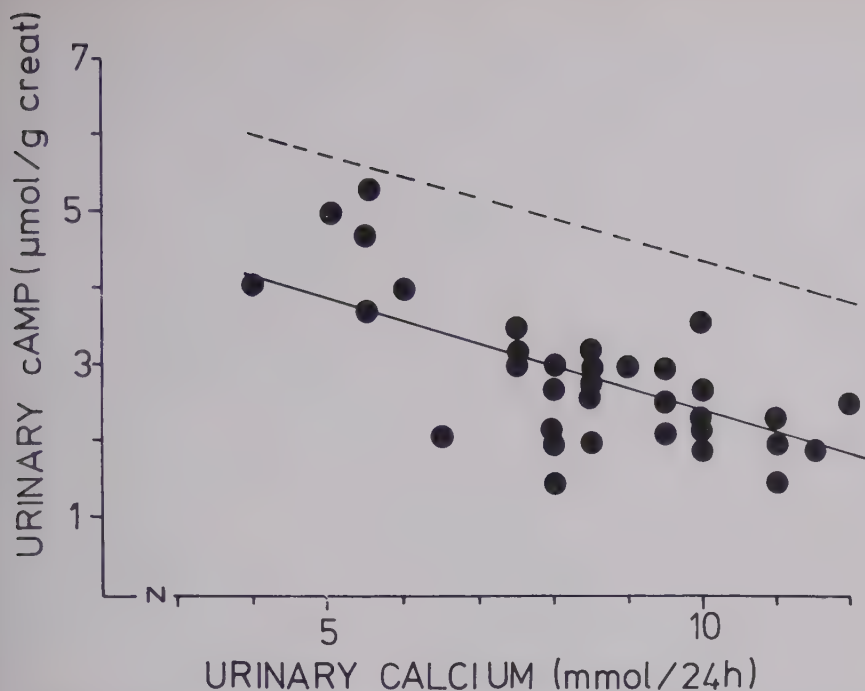


Figure 3. The relationship between the 24-hour urinary excretions of calcium and cyclic AMP (cAMP) in renal stone formers ($r = 0.49$, $p < 0.001$). The regression line for the stone formers is indicated (solid line) together with the mean + 2 S.D. limit (interrupted line) obtained from healthy controls in a previous study (Wålinder, Ljunghall & Wibell, 1977).

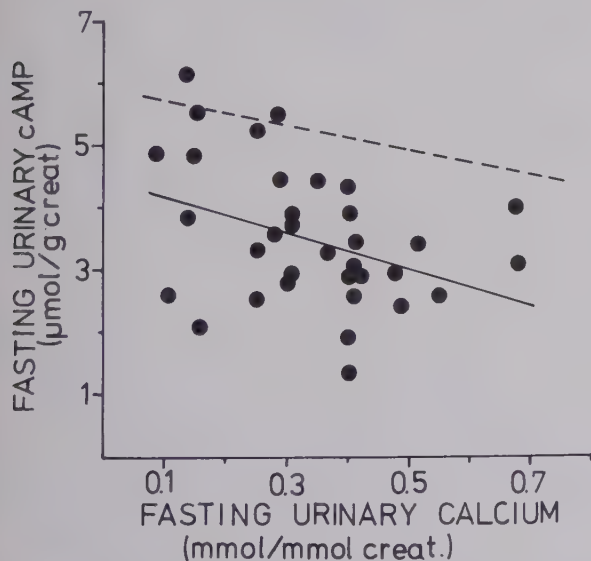


Figure 4. The relationship between the urinary excretions of calcium and cyclic AMP (cAMP) after a 12-hour fast in renal stone formers ($r = 0.38$, $p < 0.02$). The regression line for the stone formers is indicated (solid line) together with the mean + 2 S.D. limit (interrupted line) obtained from healthy controls.

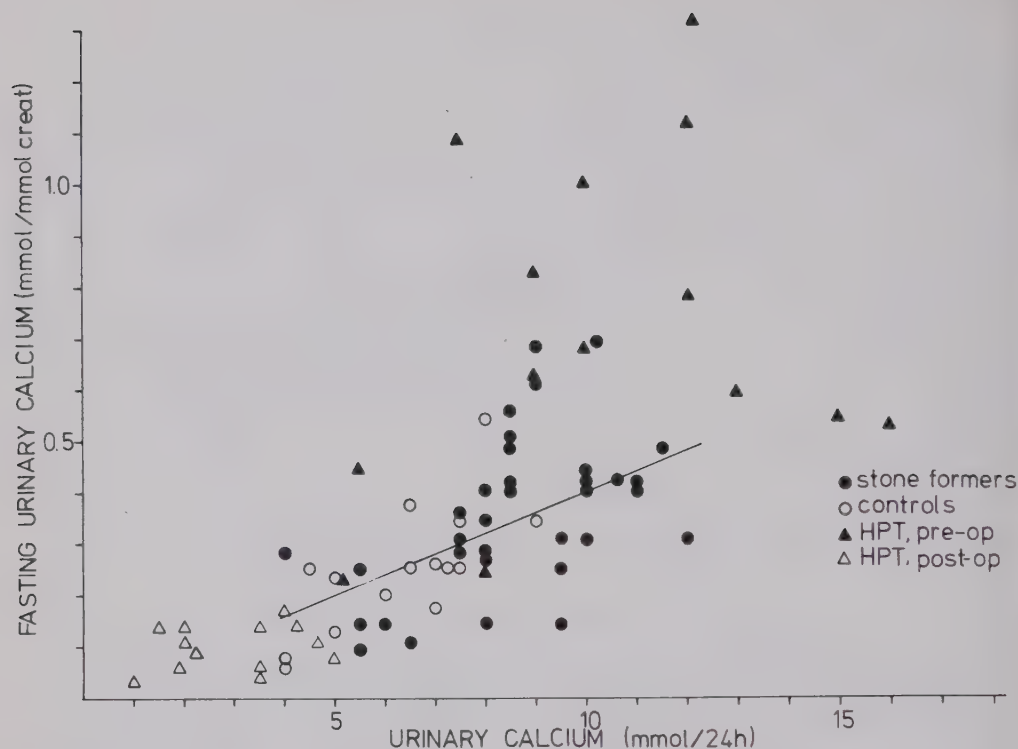


Figure 5. The relationship between the fasting and 24-hour urine calcium in renal stone formers, healthy controls and patients with hyperparathyroidism (HPT), studied immediately prior to and three months after operation. The regression line for the stone formers is indicated ($r = 0.52$, $p < 0.001$).

8 mmoles. There was no correlation between the fasting, urinary calcium and F_{Ca} ($r = 0.19$). In patients with HPT, the fasting excretion of calcium was generally raised pre-operatively and lowered post-operatively, compared with both stone formers and controls.

The urinary excretion of hydroxyproline in the fasting state was not different in stone formers and controls. In none of the groups was there any correlation to the fasting urinary calcium (Figure 6). In HPT patients the fasting urinary hydroxyproline was generally raised before the operation, particularly in those with a raised fasting urinary calcium, whereas post-operatively the excretion decreased to values within the range obtained in controls and stone formers.

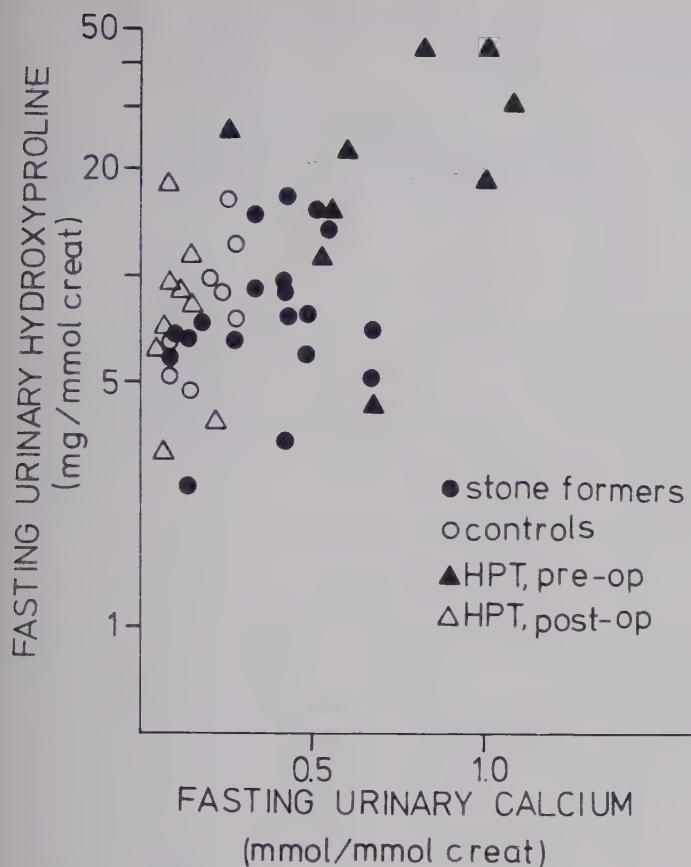


Figure 6. The urinary excretions of calcium and hydroxyproline after a 12-hour fast in renal stone formers, healthy controls and patients with hyperparathyroidism (HPT), studied immediately prior to and three months after operation.

Urinary calcium and cAMP excretion after the oral calcium load

Compared with controls, stone formers had an exaggerated increase in urinary calcium excretion after an oral calcium load of 1g. In both groups, there was a decrease of urinary cAMP (Table II, $p < 0.05$). The calcium excretion after the calcium load was correlated to F_{Ca} in stone formers ($r = 0.47$, $p < 0.01$) but not in controls ($r = 0.11$).

Serum calcium and phosphate

There were no correlations between the serum concentration of calcium or phosphate and the urinary excretions of calcium or cAMP in the fasting state,

Table III. Renal acidifying capacity and urinary excretion of beta-2-microglobulin in 34 recurrent renal stone formers

Renal acidifying capacity	Urinary beta-2-microglobulin	
	$\leq 370 \mu\text{g}/24 \text{ hours}$	$> 370 \mu\text{g}/24 \text{ hours}$
Proximal defects	2	3
Distal defects	0	2
Normal	25	2

after the oral calcium load or during the 24-hour collection, nor did the serum calcium or phosphate concentrations show any relationship with the F_{Ca} .

Renal tubular defects

Nine patients showed evidence of an impaired, renal tubular function, seven of them with acidifying defects (Table III). Compared with the other stone formers, this group did not display any significant differences in the urinary excretion of calcium or cAMP (Table IV).

DISCUSSION

In the present study, renal stone patients had a high fractional gastro-intestinal calcium absorption (F_{Ca}), together with a high 24-hour urine calcium. This gives further confirmation of the well-established relationship between calcium hyperabsorption and hypercalciuria in renal stone formers (Nordin et al, 1972; Pak, East, Sanzenbacher, Delea & Bartter, 1972; Pak, Ohata, Lawrence & Snyder, 1974; Blacklock & MacLeod, 1974). Calcium absorption varies significantly with the amount, type and form of carrier administered with the test dose (Dymling, 1971). The comparatively high value of F_{Ca} in our controls (60%) is probably mainly due to the low amount of carrier but also to some extent reflects a rather high urine calcium in our healthy subjects. The reference range for F_{Ca} in our study agrees well with that of other workers using a similar experimental design (Chanard, Assailly, Bader & Funck-Brentano, 1974; Wills et al, 1970). Since there apparently are no age-dependent differences between the ages of 20 and 60 as regards the calcium absorption (Bullamore, Gallagher, Wilkinson, Nordin & Peacock, 1970) or

Table IV. Urinary excretion of calcium and cyclic AMP in renal stone formers separated with regard to the presence of renal tubular defects. (Mean values $\pm$ S.D.)

	24-hour collection		Fasting		After calcium load	
	Urinary calcium (mmol)	Urinary cAMP (μ mol/g creat)	Urinary calcium (mmol/mmol creat)	Urinary cAMP (μ mol/g creat)	Urinary calcium (mmol/mmol creat)	Urinary cAMP (μ mol/g creat)
Tubular defects (n = 9)	8.6 $\pm$ 2.3	2.8 $\pm$ 1.0	0.32 $\pm$ 0.13	3.7 $\pm$ 1.1	0.55 $\pm$ 0.25	3.5 $\pm$ 1.1
No tubular defects (n = 25)	8.3 $\pm$ 1.9	3.1 $\pm$ 1.2	0.35 $\pm$ 0.16	3.6 $\pm$ 1.2	0.62 $\pm$ 0.14	2.8 $\pm$ 0.9

excretion (Bulusu, Hodgkinson, Nordin & Peacock, 1970; Davis, Morgan & Rivlin, 1970) no particular efforts were made to match the control group and stone formers for differences in age.

Stone formers in this study had an approximately 20% increase in F_{Ca} , compared with the controls. In addition, the values of fasting, urinary calcium in the group of stone formers were higher than in the controls, suggesting that, at least in some patients, increased bone resorption could be an additional source of the raised urinary calcium. This is based upon the assumption that the calcium appearing in the urine at zero calcium intake must be taken from body stores and presumably comes from bone (Nordin et al, 1972). The possibility that a high fasting urinary calcium may be due to an overspill of calcium from the preceding day's intake, particularly in hyperabsorbing patients, is denied by the reports that prolonged fasting does not further reduce calcium output (Nordin et al, 1972; Pak, Kaplan, Bone, Townsend & Waters, 1975). Thus, a high fasting urinary calcium might reflect bone resorption although in stone formers or controls there was no correlation to the urinary excretion of hydroxyproline, determinations of which has been reported to be useful in evaluation of metabolic bone diseases (Laitinen, 1974).

These findings of hypercalciuria, calcium hyperabsorption and possible bone resorption are in line with several other reports concerning calcium metabolism in renal stone patients. Thus, calcium-kinetic studies have indicated that stone formers have an increased bone resorption, together with an exaggerated bone formation (Lieberman, Sperling, Atsman, Frank, Modan & deVries, 1967; Anderson, Lee & Tomlinson, 1967). Several calcium balance studies have revealed slightly negative balances in hypercalciuric patients (Harrison, 1959; Jackson & Doncaster, 1959; Parfitt, Higgins, Nassim, Collins & Hilb, 1964; Edwards & Hodgkinson, 1965; Lieberman et al, 1967). A reduced bone mineral density (Alhava, Juntti & Karjalainen, 1975) and a high fasting urinary calcium (Edwards & Hodgkinson, 1965; Lieberman et al, 1967; Schwille, Schlenk, Samberger & Bornhof, 1976) have also been reported. All these data may fit into the concept of a basic disturbance of calcium metabolism in renal stone patients leading to a high turnover of calcium and with a slightly negative calcium balance (Lieberman et al, 1967). This concept would also be compatible with recent reports of elevated levels of metabolically active vitamin D, $1.25-(OH)_2$ vitamin D_3 , in some renal stone formers with hyperabsorption and hypercalciuria (Gray, Caldas, Wilz & Leman, 1976; Shen, Baylink, Nielsen, Sherrard & Haussler, 1976). However, also normal

results of measurements of bone mineral density have been reported (Pak et al, 1974) and, contrary to the findings in the present study, Nordin et al (1972) and Pak et al (1974) found that the fasting urinary calcium was almost invariably normal in hyperabsorbing stone formers.

When parathyroid activity has been investigated in normocalcemic, renal stone formers, most of the cases have displayed low values of parathyroid hormone (PTH) and cAMP (Smith & Arnaud, 1973; Pak et al, 1974; Schwille et al, 1976). On the other hand several studies have reported that, among supposedly normocalcemic individuals with hypercalciuria and recurrent renal stones, a considerable proportion may have parathyroid adenoma or hyperplasia (Wills, Pak, Hammond & Bartter, 1969; Shieber, Birge, Avioli & Teitelbaum, 1971; Johansson, Thorén, Werner & Grimelius, 1975; Muldowney et al, 1976; Eneström, Gillquist, Larsson, Sjö Dahl & Tiselius, 1976). This discrepancy may, at least partly, reflect the difficulties in determining the upper limit for normal serum calcium concentration and diagnosing borderline HPT (Yendt & Gagne, 1968; Wibell & Werner, 1973). The present study only included subjects with repeatedly normal determinations of serum calcium. Their urinary excretion of cAMP was found to be within normal limits and, on the whole inversely related to the urinary calcium output, a relationship strongly suggesting that factors other than parathyroid hyperfunction predominate in the development of hypercalciuria. Although the serum levels of calcium only vary slightly during the day, significant, post-prandial increments can be detected (MacFayden, Nordin, Smith, Wayne & Rae, 1965) particularly in hyperabsorbing, hypercalciuric individuals. This small rise in serum calcium concentration may cause an increased urinary calcium output through an overflow mechanism (Nordin et al, 1976) and is also presumably large enough to suppress the secretion of PTH and the excretion of cAMP, thereby establishing an inverse relationship between the urinary excretions of calcium and cAMP.

In this study of recurrent renal stone formers, the serum phosphate concentrations were within the normal range. A tendency to hypophosphatemia has been considered common in idiopathic hypercalciuria (Henneman et al, 1958). Since it can also be demonstrated in hypercalciuric subjects with low serum PTH concentrations (Shen et al, 1976) normocalcemic HPT is not likely to be the cause. In our population studies of stone formers (Ljunghall et al, 1977; Ljunghall & Waern, 1977), low values of serum phosphate were not a particular feature and it appears as if hypophosphatemia is an inconstant finding in

hypercalciuric stone formers (Nordin et al, 1976). Although attractive hypotheses could be proposed, for example, the activation of renal hydroxylase and the formation of metabolically active vitamin D (Gray et al, 1976; Shen et al, 1976) the role of a low serum phosphate concentration in the development of hypercalciuria may not have been fully elucidated.

Coe et al (1973) have provided evidence that many stone patients with hypercalciuria in fact have a secondary hyperparathyroidism, presumably due to a renal inability to re-absorb calcium. In the studies by Pak et al (1974, 1975, 1976) a considerably smaller proportion of stone formers, but still about 10%, fulfilled the same criteria. Among our patients nine individuals showed some evidence of an impaired renal tubular function as indicated by measurements of the renal acidifying capacity (Backman, 1976) and of the urinary excretion of beta-2-microglobulin (Peterson, Evrin & Berggård, 1969). This group did not differ significantly in any respect from other stone formers as regards the urinary excretion of calcium and cAMP. Nor were any other possible cases of the so-called "renal leak", i.e. renal hypercalciuria with secondary HPT (Pak et al, 1974), detected. If the determination of urinary cAMP is suitable for the purpose of diagnosing HPT as our own experience (Wålinder et al, 1977) and that of others (Murad & Pak, 1972; Neelon, Drezner, Borch & Lebovitz, 1973) indicate, the present study suggests that tubular defects, although commonly associated with renal stone disease (Backman, 1976), are rarely of importance in the development of hypercalciuria or secondary HPT.

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